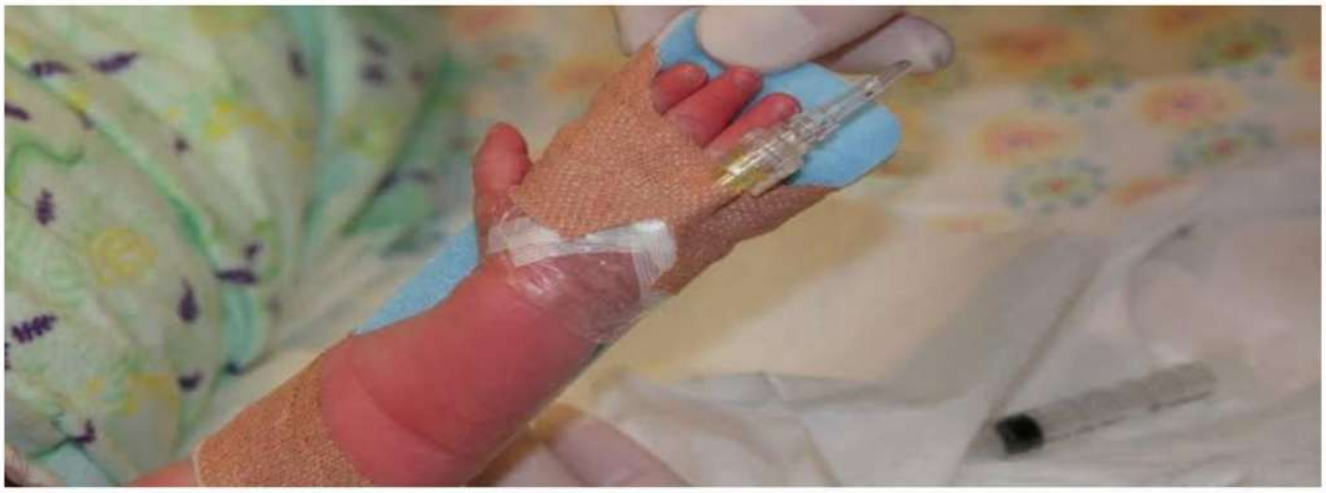

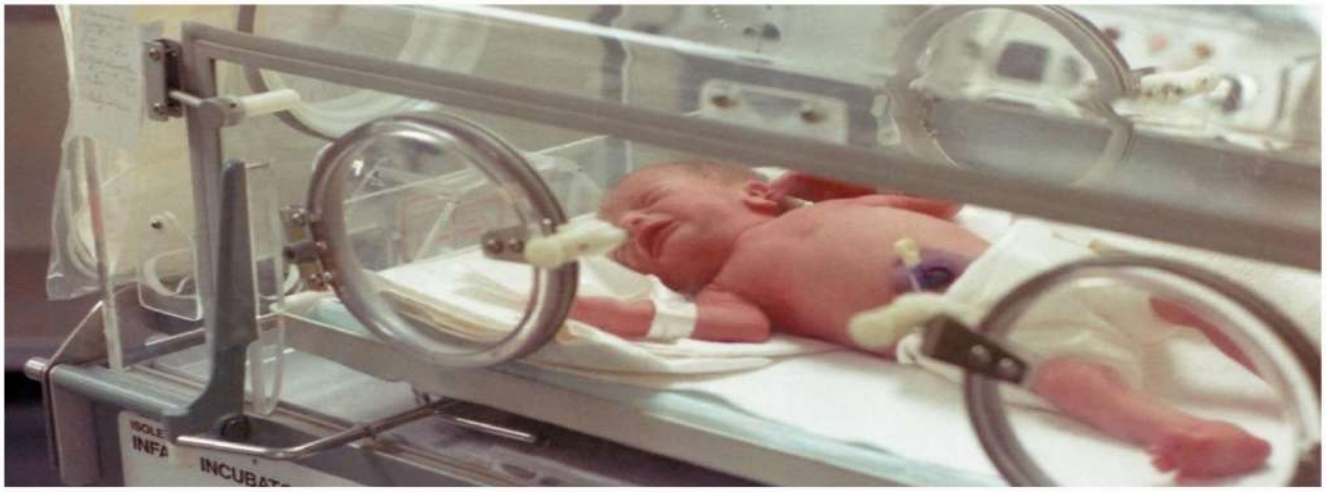

MICROMEDEX NEOFAX

NOV. 2024

Gathered By
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Neonatologist

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Micormedex NeoFax NOV. 2024

Acetaminophen

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Intravenous
Fever
Gestational age 32 weeks or more: 12.5 mg/kg/dose IV every 6 hours up to a **MAX 50 mg/kg/day** of all routes of administration [1].

Fever/Pain
Oral
Preterm infants less than 32 weeks Postmenstrual Age: 20 to 25 mg/kg orally; then 12 to 15 mg/kg/dose every 12 hours as needed or around-the-clock.
Preterm infants greater than or equal to 32 weeks Postmenstrual Age: 20 to 25 mg/kg orally; then 12 to 15 mg/kg/dose every 8 hours as needed or around-the-clock.
Term infants: 20 to 25 mg/kg orally; then 12 to 15 mg/kg/dose every 6 hours as needed or around-the-clock.

Rectal
Preterm infants less than 32 weeks Postmenstrual Age: 30 mg/kg rectally; then 12 to 18 mg/kg/dose every 12 hours as needed or around-the-clock.
Preterm infants greater than or equal to 32 weeks Postmenstrual Age: 30 mg/kg rectally; then 12 to 18 mg/kg/dose every 8 hours as needed or around-the-clock.
Term infants: 30 mg/kg rectally; then 12 to 18 mg/kg/dose every 6 hours as needed or around-the-clock.

Closure of Patent Ductus Arteriosus
Oral or IV
Preterm infants: 15 mg/kg/dose orally or IV every 6 hours for 3 days [2][3]; a second course may be required [4].

Uses

Closure of patent ductus arteriosus (PDA): NSAIDs (indomethacin and ibuprofen) are the standard drugs for closure of PDA. However, there are risks to NSAIDs and there is a high rate of spontaneous closure; therefore, treatment should be limited to select preterm newborns with symptomatic PDA [8][9]. Acetaminophen may be a treatment option in those having NSAID failure or contraindications to NSAIDs [10]. IV acetaminophen may be an option in those who have a contraindication to feeding, or who have feeding intolerance [11][4]. Oral acetaminophen appears as effective as ibuprofen, but long-term safety trials are needed [3].
A systematic review and meta-analysis of studies of preterm (less than 37 weeks

postmenstrual age) or low birth weight (less than 2500 g at birth) infants reported no significant difference in the rate of failure of PDA closure after first course of treatment for the following comparisons: Acetaminophen (oral or IV) vs ibuprofen (oral or IV; 18 studies, 1535 patients), and acetaminophen (oral or IV) vs indomethacin (IV; 4 studies, 380 patients). All cause mortality was not significantly different for either comparison, while acetaminophen was associated with a significantly lower rate of necrotizing enterocolitis compared with indomethacin (relative risk, 0.42; 95% CI 0.19 to 0.96). When comparing acetaminophen to placebo or no intervention, the rate of failure of PDA closure was significantly lower in the acetaminophen group (relative risk, 0.27; 95% CI 0.18 to 0.42; 3 studies, 240 patients), though all cause mortality was not different between groups. Early acetaminophen treatment (postnatal age less than 14 days) was associated with a significantly lower rate of failure of PDA closure compared with placebo or no intervention (relative risk, 0.35; 95% CI 0.23 to 0.53; 2 studies, 127 patients), while late acetaminophen treatment (postnatal age 14 days or older) was not associated with a lower rate of failure of PDA closure [2].

Adverse effects: Acetaminophen was associated with significantly lower rates of renal impairment (odds ratio 0.27; 95% CI, 0.09 to 0.8; 1 study), oliguria (OR 0.51; 95% CI 0.27 to 0.97; 3 studies), and hyperbilirubinemia (OR 0.46; 95% CI 0.23 to 0.94; 1 study) compared with ibuprofen in another meta-analysis. When comparing acetaminophen with indomethacin, there was no significant difference in rates of necrotizing enterocolitis (OR 0.44; 95% CI, 0.18 to 1.06; 4 studies) or other adverse effects [12]

Fever reduction and treatment of mild to moderate pain: The decision to use acetaminophen should be weighed against the epidemiological evidence of an association between acetaminophen use and asthma, atopy, rhinoconjunctivitis, or eczema; although causality has not been established [13][14][15]. The IV route may be considered when the oral or rectal route is not possible [16].

FDA Pediatric Approval
Intravenous
Management of mild to moderate pain and moderate to severe pain with adjunctive opioid analgesics in children 2 years or older. Indicated in fever in neonates or older [1].

Administration

Intravenous: Administer IV over 15 minutes (10 mg/mL). Withdraw appropriate dose and administer in bottle, bag, or IV syringe; dose should be administered within 6 hours [1]. Exercise caution when calculating the dose in milligrams and administering the dose in milliliters [5][6][7]. The administered volume in a neonate should always be 7.5 mL or less [7].

MEDICATION SAFETY

Contraindications/Precautions

Intravenous formulation **contraindicated** in patients with severe hepatic impairment or severe active liver disease. Hypersensitivity reactions, including life-threatening anaphylaxis, have been reported [18].

Rare but serious skin reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and acute generalized exanthematous pustulosis, have been associated with the use of acetaminophen. Reactions may occur after one use or at any time. Discontinue use immediately if rash or other hypersensitivity symptoms occur [19].
Use with caution in patients with hepatocellular insufficiency, severe renal insufficiency, glucose 6 phosphate dehydrogenase deficiency, chronic malnutrition, or dehydration/hypovolemia [16].
A modest reduction in blood pressure and heart rate may occur in neonates (preterm and full-term) after IV administration of acetaminophen. Neonates with pre-existing low arterial pressure may be at greater risk for hypotension [20].

Epidemiological evidence demonstrated an association between acetaminophen use and asthma [15], rhinoconjunctivitis, eczema [14] and atopy [13]. Confirmatory studies are needed; however, in a meta-analysis, the odds ratio (OR) was 1.6 (95% CI, 1.48 to 1.74) for the risk of asthma in children among users of acetaminophen in the year prior to asthma diagnosis and the first year of life and 1.96 (95% CI, 1.5 to 2.56) for the risk of wheezing and acetaminophen use in the previous year of life [15]. In 2 observational studies, the OR was 3.61 (95% CI, 1.33 to 9.77) for atopy and acetaminophen exposure before the age of 15 months [13], and up to 2.39 (95% CI, 2.24 to 2.55) for rhinoconjunctivitis symptoms or 1.99 (95% CI, 1.82 to 2.16) for eczema symptoms and acetaminophen exposure in the previous 12 months in adolescents [14]

Adverse Effects

Injection site events (pain and site reactions; 15%) and vomiting (5%) occur with IV acetaminophen [16]. Rash, fever, thrombocytopenia, leukopenia, and neutropenia have been reported in children [18][21][22][23][24]. Serious skin reactions have been reported from patients who were rechallenged with acetaminophen and had a recurrence of a serious skin reaction [19].

Hypothermia did not develop in 99 neonates (93 normothermic and 6 with fever) administered IV acetaminophen [25].

Although data are limited for neonates, in children liver toxicity occurs with excessive doses [16][18] or after prolonged administration (greater than 48 hours) of therapeutic doses. Hepatotoxicity occurred in less than 0.01% of children administered therapeutic doses of acetaminophen, in a systemic review (n=32,424; studies=62). The estimated risk for minor or major hepatic events was 0.031% (95% CI, 0.015% to 0.057%) [26]. No significant increases in liver enzymes were observed after a median duration of 60 hours (6 to 480 hours) and a median of 9 (2 to 80) doses of IV acetaminophen (20 mg/kg loading dose; 10 mg/kg (every 6 hours for more than 36 weeks postmenstrual age (PMA), every 8 hours for 31 to 36 weeks PMA, and every 12 hours for less than 31 weeks postmenstrual age) in 189 infants (1 day to 182 days of age; 30 to 55 weeks PMA), in a retrospective analysis [27].

Acute liver failure occurred in an 11-month-old boy who received therapeutic doses of oral acetaminophen for a prolonged duration (10 days) [28].

Black Box Warning

Prevent acetaminophen injection dosing errors, which may result in accidental overdose and death, by confirming that doses in milligrams (mg) are not confused with doses in milliliters (mL); that patients under 50 kg receive weight-based doses; that infusion pumps are programmed correctly; and that the total dose of acetaminophen from all routes and from all sources does not exceed daily limits. Life-threatening cases of acute hepatic failure leading to liver transplant or death have been linked with acetaminophen use. In most cases of hepatic injury, acetaminophen doses exceeded maximum daily limits and often involved the use of more than 1 acetaminophen-containing product [17].

Monitoring

Assess for signs of pain. Monitor temperature. Assess liver function. Serum acetaminophen concentration is obtained only to assess toxicity.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Nonnarcotic analgesic and antipyretic. Peak serum concentration occurs approximately 60 minutes after an oral dose. Absorption after rectal administration is variable and prolonged. Extensively metabolized in the liver, primarily by sulfation with a small amount by glucuronidation. Metabolites and unchanged drug are excreted by the kidney. Elimination half-life is approximately 3 hours in term neonates, 5 hours in preterm neonates greater than 32 weeks gestation, and up to 11 hours in more immature neonates. Elimination is prolonged in patients with liver dysfunction.

IV: A dose of 12.5 mg/kg/dose IV administered to a neonate (greater than 32 weeks gestational at birth) provided similar concentrations as those achieved in infants, children, and adolescents treated with 15 mg/kg/dose and in adults treated with a 1000-mg dose [1]. A 20 mg/kg loading dose achieved a Cmax of 15 to 25 mg/L in 19 neonates (27 to 42 weeks gestational age) included in the PARANEO study. An effect compartment concentration of 10 mg/L was associated with a pain score reduction of 3.4 units [29]. A mean plasma concentration of 11 mg/L after acetaminophen IV 10 mg/kg every 6 hours (with or without a 20 mg/kg loading dose) was predicted from a pharmacokinetic analysis of 158 neonates (32 to 44 weeks postmenstrual age) [30].

Based on a population pharmacokinetic analysis of 220 patients varying from preterm infants through adults, the following table provides IV doses to achieve an acetaminophen concentration of 9 mg/L and pharmacokinetic parameters [31]:

Acetaminophen (population pharmacokinetics)					
	To Achieve Target Average Acetaminophen Concentration of 9 mg/L		Pharmacokinetic parameters		
Weight range (kg)	Loading Dose IV (mg/kg)	Maintenance Dose IV every 6 hours (mg/kg)	Cl (L/hr)	Vd (L)	half-life (hrs)
0.5 to 1	11.2	5.1	0.047	0.18	2.6
1 to 1.5	12.1	6	0.11	0.36	2.2
1.5 to 2	12.2	6.8	0.19	0.54	2
2 to 3	13.3	7.4	0.27	0.72	1.8
3 to 5	12.8	8.5	0.47	1.08	1.6
5 to 8	13.5	10.4	0.96	1.79	1.3
8 to 9	16.1	12.4	1.8	2.87	1.1
9 to 15	16.8	12.9	2.1	3.23	1
15 to 20	19.2	14.8	4.1	5.38	0.9
20 to 35	18.4	15.4	5.7	7.17	0.9
35 to 50	18.3	15.2	9.9	12.55	0.9
50	17.4	14.5	13.4	17.93	0.9

Oral/Rectal: Target concentrations above 10 mg/L are predicted in 50% of patients administered acetaminophen (30 mg/kg orally loading dose, 15 mg/kg/dose orally every 8 hours and 37.5 mg/kg rectally loading dose, 20 mg/kg/dose every 8 hours) in a population pharmacokinetic analysis (n=30, 1 to 90 days old, 31 to 40 weeks gestational age) [32].

ABOUT

Special Considerations/Preparation

Oral: Available orally in various liquid formulations containing 160 mg/5 mL (32 mg/mL), 80 mg/0.8 mL (100 mg/mL), and 500 mg/15 mL (33.33 mg/mL). Some formulations are alcohol, dye, and sugar free.
Rectal: Suppositories strengths are 80,120, 325, and 650 mg. Inaccurate dosing may occur with rectal administration because of unequal distribution of acetaminophen in the suppositories.

Injection: Intravenous formulation available in a 100-mL glass vial containing 1000 mg (10 mg/mL). Do not refrigerate or freeze. Vial is for single use only and should be used within 6 hours of opening. [18]. However, IV acetaminophen remained stable for up to 84 hours at room temperature when withdrawn into syringes (100 mg, 250 mg, and 500 mg) and in the original vial (250 mg and 900 mg). Sterility was not tested [33].

Extemporaneous Preparation
50 mg/mL Oral Suspension

- Measure 5 g acetaminophen; reduce particle size to a fine powder [34].
- Add a small portion of SyrSpend SF PH 4 to form a smooth paste [34].
- Add sufficient SyrSpend SF PH 4 geometrically, mixing after each addition, to a final volume of 100 mL [34].
- Package in a tight, light-resistant container and label to shake well before use [34].
- Use a beyond-use date of up to 90 days when packaged in low actinic, light-resistant containers and stored at room temperature or refrigerated temperatures [34].

DOSING/ADMINISTRATION

Dose

Metabolic Alkalosis: 5 mg/kg IV every 6 to 8 hours [1][2][3][4]

Posthemorrhagic Ventricular Dilation, Adjunct; Prevention of Shunt Placement: Ineffective and associated with increased neurologic morbidity compared with standard of care [5].

Uses

Metabolic Alkalosis:
Retrospective studies of critically ill neonates and pediatric patients with metabolic alkalosis have reported that acetazolamide is effective at significantly reducing pH and serum bicarbonate, and significantly increasing serum chloride measurements; however, clinical outcomes have generally not been reported [8][1][2][3][4][9]. Dosages studied in neonates include 5 mg/kg IV every 6 to 8 hours [1][4], 30 mg/kg/day IV in 3 or 4 divided doses [2], 5 mg/kg IV or orally once daily for 3 days [9], and 3 to 5 mg/kg IV every 6 hours for 4 doses within 24 hours [3].

Posthemorrhagic ventricular dilation (PHVD), adjunct; Prevention of shunt placement: Use of acetaZOLAMIDE and furosemide in preterm infants with PHVD was associated with a higher rate of shunt placement, death, and increased neurological morbidity as compared to standard therapy alone, in a multicenter, randomized, controlled trial (n=177). Infants less than 3 months beyond the expected date of delivery and with a ventricular width more than 4 mm above the 97th percentile after intraventricular hemorrhage received either standard therapy plus acetaZOLAMIDE 100 mg/kg daily and furosemide 1 mg/kg daily (n=88) or standard therapy alone (n=89). Mean gestation age was 28.5 weeks and median postnatal age was 23.5 days in the drug therapy group. Median treatment duration of acetaZOLAMIDE was 35 days. Assessments at 1 year showed that death or shunt placement had occurred in 56 infants (63.3%) in the drug therapy group and in 46 (52.2%) allocated to standard therapy (11.1% (CI, -3.2% to 25.2%; p=0.15). Adverse effects were reported in 38 infants, 23 of whom required permanent discontinuation of drug therapy [5]. In a small cohort study, 9 of 10 preterm infants with raised intracranial hypertension secondary to PVHD treated with acetaZOLAMIDE and furosemide avoided placement of a ventriculoperitoneal shunt; in comparison, 3 of 6 patients who received serial lumbar puncture avoided shunt placement. acetaZOLAMIDE was started at 20 mg/kg/day and increased by 10 mg/kg up to 100 mg/kg/day in 3 divided doses administered orally or if necessary, IV; dose of furosemide was 1 mg/kg daily orally or IV. Mean gestational age was 28.4 weeks [10]. Limited use of acetaZOLAMIDE may be warranted in infants with PVHD and raised intracranial hypertension based on the findings of Kennedy et al, 2001 [5].

Pediatric FDA Approved Indications
Oral extended-release capsules:
Indicated in patients 12 years or older for the prevention or amelioration of symptoms associated with acute mountain sickness despite gradual ascent. Also indicated in patients 12 years or older as adjunctive treatment of open-angle glaucoma, secondary glaucoma, and preoperatively in acute closed-angle glaucoma when delay of surgery is indicated in order to lower intraocular pressure. Safety and efficacy of oral extended-release capsules not established in pediatric patients younger than 12 years [11].

IV and oral immediate-release:
Safety and efficacy of IV injection [12] and oral immediate-release tablets [13] not established in pediatric patients.

Administration

IV Injection: IV route preferred; IM use not recommended [6]. Recommended concentrations for intermittent IV are 50 mg/mL or 100 mg/mL [7].

MEDICATION SAFETY

Contraindications/Precautions

Contraindications
Chronic noncongestive angle-closure glaucoma; long-term use may mask symptoms of worsening glaucoma [12][11][13]
Cirrhosis or marked liver disease or dysfunction ; risk of hepatic encephalopathy [12][11][13]
Hyperchloremic acidosis [12][11][13]
Hypersensitivity to sulfonamides or other sulfonamide derivatives; cross-sensitivity may occur [12][11]
Hypokalemia [12][11][13]
Hyponatremia [12][11][13]
Renal dysfunction or marked disease [12][11][13]
Suprarenal gland failure [12][11][13]

Precautions
Concomitant Use: Use with other carbonic anhydrase inhibitors is not recommended [11]
Concomitant Use: Use caution in patients also receiving high-dose aspirin; anorexia, tachypnea, lethargy, coma, and death have been reported [13][13][11].
Endocrine and Metabolic: Electrolyte and acid/base imbalances may occur, especially in patients with diabetes mellitus or impaired glucose tolerance; monitoring recommended [12][11]
Hematologic: Blood dyscrasias such as agranulocytosis and aplastic anemia, with fatal cases, have been reported with sulfonamides; monitoring recommended and discontinuation

may be necessary [12][11][13]
Immunologic: Hypersensitivity reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, anaphylaxis, and blood dyscrasias, with fatal cases, have been reported with sulfonamides; discontinue if hypersensitivity or other serious reactions occur [12][11][13]
Renal: Patients with impaired renal function may experience electrolyte and acid/base imbalances [11]
Respiratory: Pulmonary obstruction or emphysema patients, especially with alveolar ventilation impairment, may experience precipitated or aggravated acidosis [12][11][13]
Respiratory: Give cautiously to patients with alveolar ventilation impairment as electrolyte and acid/base imbalances may occur [11][13]

Adverse Effects

Nephrocalcinosis, per renal ultrasound, occurred more frequently in the acetaZOLAMIDE/furosemide group than standard therapy group (24% vs 4% (difference 19%, CI 9% to 30%), in a randomized, controlled trial (n=177) of preterm infants (mean gestation age 28.5 weeks and median postnatal age was 23.5 days) with post-hemorrhagic ventricular dilation. Median treatment duration of acetaZOLAMIDE was 35 days. [5]. Hypercalciuria occurred in 7 of 12 infants exposed to furosemide and acetaZOLAMIDE; nephrocalcinosis developed in 5 of the 7 patients with hypercalciuria [10]. A transient increase in intracranial pressure was demonstrated in 6 of 8 infants (25 to 37 weeks gestation, 16 to 121 postnatal days) with post-hemorrhagic hydrocephalus administered IV acetaZOLAMIDE 50 mg/kg. No increase was observed with oral administration. In all 4 preterm infants with chronic lung disease, discontinuation of acetaZOLAMIDE (IV and oral) was necessary due to the inability to compensate for the rise in pCo_2[16].

Black Box Warning

Severe reactions to sulfonamides (eg, Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias) have occurred, rarely resulting in fatality. Sensitizations may recur. Discontinue use if hypersensitivity or other serious reactions occur. Anorexia, tachypnea, lethargy, coma, and death have been reported with concomitant high-dose aspirin and acetaZOLAMIDE [15].

Monitoring

Toxic Laboratory Monitoring

Obtain a CBC and platelet count at baseline and at regular intervals during therapy [12][11].
Monitor electrolytes periodically during therapy [12][11].
Consider monitoring urinary pH in patients on acetaZOLAMIDE concomitantly with other antiepileptic drugs, particularly valproate [14].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action: acetaZOLAMIDE, a nonbacteriostatic sulfonamide, inhibits carbonic anhydrase from catalyzing the reversible hydration of carbon dioxide and dehydration of carbonic acid. In the eye, carbonic anhydrase inhibition reduces aqueous humor production resulting in a decrease in intraocular pressure. It also delays abnormal, paroxysmal excessive discharge from CNS neurons and affects promotion of diuresis and urinary alkalinization [6][17][15].

ABOUT

Special Considerations/Preparation

IV Injection
Availability: Available as an IV lyophilized powder for solution containing acetaZOLAMIDE 500 mg/vial [6].
Storage: Store vials at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F). Reconstituted solution is stable (ie, retains physical and chemical properties) for 3 days under refrigeration between 2 and 8 degrees C (36 and 46 degrees F) or 12 hours when stored at a room temperature between 20 and 25 degrees C (68 and 77 degrees F) [12].

Oral Extended-Release Capsule
Availability: Available as an oral extended-release capsule containing acetaZOLAMIDE 500 mg [17].
Storage: Store at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F) [11].

Oral Tablet
Availability: Available as an oral tablet containing acetaZOLAMIDE 125 mg or 250 mg; also contains lactose monohydrate [15].
Storage: Store in a tightly closed container at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F) [13].

Preparation
IV Injection: Prior to use, reconstitute each 500-mg vial with at least 5 mL of sterile water for injection [6].

Extemporaneous Compounding:
acetaZOLAMIDE 25 mg/mL in a 1:1 mixture of ora-sweet and ora-plus, in a 1:1 mixture of ora-sweet SF and ora-plus, and in cherry syrup (concentrated cherry syrup diluted 1:4 with simple syrup) was stable for up to 60 days at 5 and 25 degree C. The liquids were protected

from light [18].
acetaZOLAMIDE 25 mg/L in 70% sorbitol solution with a suspension vehicle, sweeteners, flavoring agents, preservatives, humectants, and pH adjusters was stable for at least 79 days at 5, 22, and 30 degrees C. Maintain at a pH 4 to 5 and protected from light. The following are directions for compounding 300 mL of a 25 mg/mL acetaZOLAMIDE suspension (alexander, 1991)[19]:

- Triturate 30 acetaZOLAMIDE 250-mg tablets in a glass mortar.
- Slowly add approximately 30 mL of 70% sorbitol solution and levigate the powder.
- Slowly add 1.5 g of sodium carboxymethylcellulose to 50 mL of warm purified water, USP, and allow the mixture to hydrate for 15 to 20 minutes.
- Add 1.5 g of aluminum magnesium silicate to a separate 50 mL portion of purified water, USP.
- Combine the hydrated sodium carboxymethylcellulose and dispersed aluminum magnesium silicate with the levigated powder in the glass mortar.
- Geometrically incorporate 60 mL of syrup, USP, 7.5 mL of glycerin, USP, and 6 mL of paraben stock solution (2.5% methylparaben and 1% propylparaben in propylene glycol) with constant agitation until a homogeneous mixture forms.
- Transfer contents of mortar to a 500-mL graduated cylinder.
- Add 0.015 g of FD&C Red No. 40 and 0.3 mL of strawberry flavor.
- Rinse the mortar with a 30-mL portion of purified water, USP, and transfer to a graduated cylinder. Repeat this step until the volume of the liquid reaches 300 mL.
- Homogenize utilizing a suitable blender.
- Adjust the pH to 5 using 36% w/w hydrochloric acid (usually 1 to 3 drops).
- Transfer into an amber glass bottles with constant stirring. Add a "Shake well before using" auxiliary label.

DOSING/ADMINISTRATION

Dose

Acetaminophen Overdose, Acute

Loading Dose Protocol

If the time of acute acetaminophen ingestion is unknown, **administer a loading dose immediately**, and use acetaminophen concentration levels to determine need for continued treatment [1][2].

If acetaminophen concentrations cannot be obtained or are uninterpreted within 8 hours of acetaminophen ingestion or signs of acetaminophen toxicity are present, **administer a loading dose immediately** and continue treatment [1][2].

If the patient presents more than 8 hours after ingestion and the time of ingestion is known, **administer a loading dose immediately** and use acetaminophen concentration levels to determine the need for continued treatment [1][2].

To determine if acetylcysteine is indicated, a revised Rumack-Matthew nomogram based on blood acetaminophen concentrations relative to ingestion time can be utilized between 4 and 24 hours after an acute ingestion. Levels drawn earlier than 4 hours from ingestion are not appropriate for use, and use of the nomogram is not indicated in the setting of repeated supratherapeutic ingestion extending beyond 24 hours, at which point treatment should be initiated if the level is 20 mcg/mL or greater or if transaminase levels (AST/ALT) are abnormal and other findings are consistent with acetaminophen toxicity [3].

Revised Rumack-Matthew Nomogram for the Acute Ingestion of Acetaminophen		
Time Since Ingestion (hours)	Acetaminophen Concentration Requiring Treatment*	Acetaminophen Concentrations Defined as High-Risk^
4	150 mcg/mL	300 mcg/mL
8	70 mcg/mL	150 mcg/mL
12	35 mcg/mL	75 mcg/mL
16	18 mcg/mL	35 mcg/mL
20	9 mcg/mL	18 mcg/mL
24	4.5 mcg/mL	9 mcg/mL
*Treatment is indicated when acetaminophen level is at or above the listed concentration at a given time point since ingestion; ^levels indicate an increased risk of liver injury		
Levels drawn earlier than 4 hours from ingestion are not appropriate for use with the nomogram, nor is it indicated in the setting of repeated supratherapeutic ingestion extending beyond 24 hours		

- If acute overdose was from extended-release formulation and the acetaminophen level is below the possible toxicity line but greater than 10 mcg/mL at 4 to 12 hours post ingestion, **draw a second sample 4 to 6 hours** after the first level was drawn.
- If acetaminophen concentrations are below the possible toxicity line, but time of ingestion is unknown or sample was taken less than 4 hours post ingestion, **administer a loading dose**.
- If acetaminophen concentrations are below the possible toxicity line, time of ingestion is known, and the sample was taken more than 4 hours post ingestion, **do not administer acetylcysteine** as the probability of hepatotoxicity is minimal.

Maintenance Dose Protocol[1][2]
Determine the need for continued therapy after the loading dose, based on the acetaminophen concentration:

- If the acetaminophen concentration is above the possible toxicity line according to the nomogram, or if the concentration was not obtained, **continue treatment** with the maintenance dose.
- If the acetaminophen concentration is below the possible toxicity line, the time of ingestion is known, and the sample was taken more than 4 hours post ingestion, **discontinue treatment**.
- If the acetaminophen concentration was in the non-toxic range, but time of ingestion is not known or less than 4 hours, **obtain a second sample** and consider clinical condition of patient in deciding whether to continue treatment. A complete treatment course if recommended if there is any uncertainty regarding the patient's risk for hepatotoxicity.

Continued Therapy Following Completion of Loading and Maintenance Doses Protocol [2]

- Consider therapy beyond the loading and maintenance doses in cases of suspected massive overdose, with concomitant ingestion of other substances, or in patients with preexisting liver disease.
- If acetaminophen levels are still detectable following the last maintenance dose, or if ALT/AST levels are still increasing or the INR remains elevated, continue maintenance doses and contact a United States regional poison center at 1-800-222-1222 or the special health professional assistance line for acetaminophen overdose at 1-800-525-6115.

Oral
Effervescent Tablets and Oral solution
Loading dose: 140 mg/kg orally [1][4]
Maintenance doses: 70 mg/kg orally every 4 hours for 17 doses starting 4 hours after loading dose [1][4].

IV
Loading dose: 150 mg/kg IV in 3 mL/kg for those weighing *5 kg or more* administered over 1 hour. Adjust the total IV volume, as clinically necessary, to avoid fluid overload [5][6][7][2].
Second dose: 50 mg/kg IV in 7 mL/kg for those weighing *5 kg or more* administered over 4 hours. Adjust the total IV volume, as clinically necessary, to avoid fluid overload [5][6][7][2].
Third dose: 100 mg/kg IV in 14 mL/kg for those weighing *5 kg or more* administered over 16 hours. May continue beyond 21 hours if clinically indicated. Adjust the total IV volume, as clinically necessary, to avoid fluid overload [5][6][7][2].

Repeated Supra-therapeutic Acetaminophen Ingestion
Effervescent Tablets: Rumack-Matthew nomogram does not apply. Contact regional poison center (1-800-222-1222) or a special health professional assistance line for specific dosage and administration information [1].

Uses

Acetaminophen overdose: For specific treatment management call 1-800-222-1222 (regional poison center) or 1-800-525-6115 (special health professional assistance line) [8]. To determine if acetylcysteine is indicated, a revised Rumack-Matthew nomogram based on blood acetaminophen concentrations relative to ingestion time can be utilized between 4 and 24 hours after an acute ingestion. Levels drawn earlier than 4 hours from ingestion are not appropriate for use, and use of the nomogram is not indicated in the setting of repeated supratherapeutic ingestion extending beyond 24 hours, at which point treatment should be initiated if the level is 20 mcg/mL or greater or if transaminase levels (AST/ALT) are abnormal and other findings are consistent with acetaminophen toxicity[3].
Data in neonates treated with acetylcysteine are limited to case reports [9][10][5][6][7][11] with ages ranging from 1 day of age (3.78 kg) [11] to 22 days of age (4.1 kg) [5], including preterm neonates as young as postmenstrual age 27.3 weeks (12 days of age; weight 940 grams) [10]. All neonates experienced full recovery with most experiencing no evidence of liver toxicity during and after the course of acetylcysteine treatment. Although neonates may not be as susceptible to liver injury compared to children or adults due to differences in hepatic development, acetylcysteine is the standard treatment.

Gastric Lactobezoar: A gastric lactobezoar was successfully treated after 4 doses of acetylcysteine 10 mg/kg/dose via nasogastric (NG) tube every 6 hours in a 1 month of age full-term infant. Each dose was diluted in 50 mL of normal saline and administered over 30 minutes, then the NG tube was clamped for 2 hours, followed by aspiration at 3 and 6 hours after the dose [12].

Lung Disease, Non-Cystic Fibrosis: Evidence is limited and does not support the use of oral or inhaled acetylcysteine for non-cystic fibrosis lung disease such as primary ciliary dyskinesia, chronic lung disease of infancy, pneumonia, asthma, atelectasis, inhalation injury, or lower respiratory tract infection in pediatric patients or neonates [13]. A 6-day course of IV acetylcysteine (16 to 32 mg/kg/day) started before the age of 36 hours did not improve mortality, the incidence of bronchopulmonary dysplasia, or lung function in a randomized, double-blind, placebo-control trial (n=391; weight range 500 to 999 g) [14][15]. Furthermore, harm was demonstrated in 10 ventilated premature infants with chronic lung disease and treated with intratracheally administered acetylcysteine for 7 days [16].

Pediatric FDA Approved Indications
Inhalation Solution:
Indicated as adjuvant therapy for patients with abnormal, viscid, or inspissated mucous secretions in several conditions, including [4]:

- Acute bronchopulmonary disease
- Atelectasis due to mucous obstruction

- Chronic asthmatic bronchitis
- Chronic respiratory disease
- Diagnostic bronchial studies
- Post-traumatic chest conditions
- Pulmonary complications of cystic fibrosis
- Respiratory complication of surgical procedure
- Tracheostomy care
- Use during anesthesia

Oral/IV Solution:
Indicated as an antidote to prevent or lessen hepatic injury that may occur following the ingestion of a potentially hepatotoxic quantity of acetaminophen [4] in patients with acute ingestion or from repeated supratherapeutic ingestion [2].
Effervescent Tablets:
Indicated as an antidote to prevent or lessen hepatic injury that may occur following the ingestion of a potentially hepatotoxic quantity of acetaminophen in patients with acute ingestion or repeated supra-therapeutic ingestion (exposure to higher than recommended dosages for extended periods of time) [1].

Administration

Effervescent Tablet: Dissolve two 2.5-gram tablets in 100 mL of water for a 50 mg/mL solution [1]
Administer immediately or within 2 hours of preparation once tablets are dissolved. If vomiting occurs within 1 hour of administration, repeat dose. May be administered by nasoduodenal tube [1].

Oral Solution: Dilute the 20% solution with diet cola or other diet soft drink to a final concentration of 5% (add 3 mL of diluent for each 1 mL of 20% solution; do not decrease the proportion of diluent). If administered via gastric tube or Miller-Abbott tube, water may be used as the diluent. Administer within 1 hour of dilution. Repeat dose if patient vomits within 1 hour of administration. Dilution may minimize vomiting. May be administered by duodenal intubation if persistent vomiting is present. **Not for parenteral injection** [4].
If activated charcoal has been administered, then gastric lavage must be performed before administration of oral acetylcysteine [4].

IV Solution: Acetadote® is hyperosmolar (2600 milliosmoles/liter [mOsmol/L]) and the osmolarity of the solution is increased as the diluent volume is decreased; adjust osmolarity to physiologically safe level, generally not less than 150 mOsmol/L in children [8].

Examples of Acetadote(R) Concentration and Osmolarity in 3 Solutions

Acetylcysteine Concentration	Osmolarity		
	Sterile Water for Injection	1/2 Normal Saline	D5W
7 mg/mL	91 mOsmol/L*	245 mOsmol/L	343 mOsmol/L
24 mg/mL	312 mOsmol/L	466 mOsmol/L	564 mOsmol/L
* Adjust osmolarity to a physiologically safe level (generally not less than 150 mOsmol/L for pediatric patients)			
Acetylcysteine IV injection product information, 7/2016			

Concentration of vial is 200 mg/mL. See Dose Section for rate and infusion concentration [8].

MEDICATION SAFETY

Contraindications/Precautions

Inhalation solution: Liquefied bronchial secretions may increase in volume, leading to airway obstruction if cough is inadequate; mechanical suction may be required. Bronchospasm may occur in asthmatics. As increased concentration of drug may occur from solvent evaporation, dilution of nebulizing solution with appropriate amounts of sterile water for injection is recommended [4].

IV solution: Acute flushing and erythema may develop, usually within 30 to 60 minutes after initiating therapy and usually will spontaneously resolve. However, serious acute hypersensitivity reactions, including fatal cases, have been reported. Use with caution in patients with asthma due to risk of bronchospasm. In patients less than 40 kg and for those requiring fluid restriction, fluid overload potentially leading to hyponatremia, seizure, and death may occur; therefore, diluent volume needs to be adjusted [2].
Oral solution: If encephalopathy due to hepatic failure occurs, discontinue treatment to avoid further exposure to nitrogenous substances. Evaluate risk versus benefit in patients at risk of gastric hemorrhage (eg, esophageal varices, peptic ulcer) due to increased vomiting with treatment [4].

Adverse Effects

IV infusion of acetylcysteine did not produce adverse effects in one study of preterm newborns (n=10; gestational age, 25 to 31 weeks; weight, 500 to 1380 g) when administered at a mean rate of 4.2 mg/kg/hr for 24 hours, or in a second study of newborns (n=6; gestational age, 26 to 30 weeks; weight, 520 to 1335 g) when administered at a rate of 0.1 to 1.3 mg/kg/hr for 6 days [8].
Hypernatremia developed in a preterm infant (30 weeks gestation) administered oral

acetylcysteine solution (33.5 mmol/kg/day sodium from acetylcysteine) for meconium ileus. Sodium concentration returned to normal after acetylcysteine was discontinued [17].

Solution Compatibility

D_5 W; 0.45%NaCl.

Terminal Injection Site Compatibility

Acetylcysteine 100 mg/mL
Vancomycin 10 mg/mL.

Terminal Injection Site Incompatibility

Cefepime, ceftazidime.

Compatibility information refers to physical compatibility and is derived from Trissel's™ 2 Clinical Pharmaceutics Database. The determination of compatibility is based on concentrations for administration recommended herein. Drug compatibility is dependent on multiple factors (eg, drug concentrations, diluents, storage conditions). This list should not be viewed as all-inclusive and should not replace sound clinical judgment. The user is referred to Trissel's™ 2 for more complete details.
Trissel's™ 2 Clinical Pharmaceutics Database, version updated on 06/15/2013.

Monitoring

Inhalation Therapy: Monitor patients with asthma closely during inhalation therapy. Monitor renal and hepatic function and electrolytes throughout therapy [4].

IV/Oral Therapy for Overdose:
Obtain plasma or serum acetaminophen levels prior to detoxification. For acute ingestion, obtain as early as possible but no sooner than 4 hours postingestion [1][2].
If extended-release acetaminophen was ingested and the acetaminophen concentration at 4 hours post ingestion was below the possible toxicity line, draw a second sample at 8 to 10 hours post ingestion [1][2] or 4 to 6 hours after the first level was drawn [3].
Assess hepatic function (AST, ALT, bilirubin, INR, prothrombin time), renal function (creatinine and BUN), blood glucose, and electrolytes prior to detoxification, and throughout treatment [1][2]; assess hepatic function at least every 12 to 24 hours [3].
Assess acetaminophen levels as needed during treatment to determine need for continued

therapy [1][2], at least every 12 to 24 hours [3].
Assess acetaminophen levels, ALT/AST, and INR after the last maintenance dose [1][2].
Carefully monitor patients with asthma or with a history of bronchospasm during initiation and throughout therapy [1][2].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Systemic: Acetylcysteine may protect against acetaminophen overdose-induced hepatotoxicity by maintaining or restoring hepatic concentrations of glutathione, or by acting as an alternate substrate for conjugation with reactive acetaminophen metabolites [1][2].
Glutathione is required to inactivate an intermediate metabolite of acetaminophen that is thought to be hepatotoxic. In acetaminophen overdose, excessive quantities of this metabolite are formed because the primary metabolic pathways (glucuronide and sulfate conjugation) become saturated. CYP2E1 then metabolizes a larger fraction of the ingested dose to form an increased amount of the toxic metabolite [4].
Metabolism of acetylcysteine is believed to form cysteine and disulfides (N,N-diacetylcysteine and N-acetylcysteine), with further metabolism of cysteine to form glutathione and other metabolites. Acetylcysteine steady-state Vd and protein binding were 0.47 L/kg and 66% to 87%, respectively. Urinary recovery was 13% to 38% within 24 hours of a single oral dose. Mean total body clearance was 0.11 L/hr/kg with an estimated renal clearance of 30% of the total. Mean half-life was 5.6 hours [1][2].
Mean elimination half-life was longer in premature newborns (11 hours) compared with adults (terminal half-life, 5.6 hours) [18]. Clearance (32 to 62 mL/kg/hr) and Vd (167 to 1010 mL/kg) were correlated with weight and gestational age in 10 neonates (mean 27.7 weeks gestation; mean 863 grams) started on 4.2 mg/kg/hr IV acetylcysteine soon after birth; half-life did not correlate with either parameter. A mean steady-state concentration of 161 micromole/L was attained within 2 to 3 days in 5 of 6 neonates (mean 27.6 weeks gestation; mean 894 grams) started on 0.3 to 1.3 mg/kg/hr IV acetylcysteine at the age of 24 hours and continued for a duration of 6 days [18].
]**Inhalation:** Acetylcysteine exerts its mucolytic action through its free sulfhydryl group, which opens the disulfide linkage in mucus and lowers its viscosity. This action increases with increasing pH and is most significant at pH 7 to 9. The mucolytic action of acetylcysteine is not affected by the presence of DNA [4].

ABOUT

Special Considerations/Preparation

Effervescent Tablets:
Supplied as 500 mg or 2.5 g effervescent tablets for oral solution. Dissolve effervescent tablets and use within 2 hours [1].

Store at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F). Store in original packaging until ready for use and protect from moisture [1].

IV Injection: Available as a 20% IV solution containing acetylcysteine 200 mg/mL in 30-mL single-dose vials [8].
A color change of the solution to slight pink or purple may occur once the vial is punctured, but product quality is not affected. Contains no preservatives. Discard unused solution left in vial after opening. Diluted solution may be stored at room temperature for up to 24 hours [8].

Oral/Inhalation Solution: Available in 10-mL and 30-mL vials of a 10% (100 mg/mL) or 20% (200 mg/mL) acetylcysteine sodium sterile, unpreserved solution for oral or inhalation use (not for injection). Do not mix with antibiotics such as tetracycline, oxytetracycline, or erythromycin lactobionate. Opened vial may be refrigerated for up to 96 hours [4].
Acetylcysteine inhalation therapy was chemically unstable with dornase alfa. Although chemically stable together, aerosol characteristics have not been studied when the following were combined with acetylcysteine cromolyn, salbutamol, ipratropium, or colistimethate sodium [19].

DOSING/ADMINISTRATION

Dose

Herpes Simplex Virus Infection, Treatment and Preemptive Therapy
FDA-Approved Dosage
Less than 34 weeks postmenstrual age: 20 mg/kg IV every 12 hours for 21 days; infuse each dose at a constant rate over 1 hour [1]
Postmenstrual age 34 weeks or older: 20 mg/kg IV every 8 hours for 21 days; infuse each dose at a constant rate over 1 hour [1]
Infections of the CNS, Skin, Eye, Mouth, or Disseminated
Population based pharmacokinetic/pharmacodynamic data supports alternative frequency of administration. See USES section for details.[2]
Off-label Dosage
Less than 30 weeks postmenstrual age: 20 mg/kg IV every 8 [3][4][5] to 12 hours [2].
30 weeks or more postmenstrual age: 20 mg/kg IV every 8 hours [6][4][2][5].
Treat localized herpes simplex disease for 14 days and disseminated or CNS disease for 21 days [6][4][5]. For CNS disease, continue IV therapy for another 7 days, when repeat DNA polymerase chain reaction (cerebrospinal fluid herpes simplex virus) is positive after 19 to 21 days of acyclovir therapy. Continue IV therapy until PCR is negative [6]. The duration for preemptive therapy without proven disease is 10 days [5].

Herpes Simplex Virus Infection (CNS, Disseminated Disease, Skin, Eye, or Mouth), Chronic suppression: 300 mg/m^2/dose orally 3 times a day when disease is severe and recurrent. Begin suppressive therapy immediately after completion of IV treatment and continue for 6 months [6][7][8].

Varicella-Zoster Virus Infection: 10 to 15 mg/kg/dose IV every 8 hours for 5 to 10 days [9][10][11][12].

Dose Adjustments
Preterm infant less than 33 weeks gestational age: give usual IV dose every 12 hours [13].

Renal
CrCl 25 to 50 mL/min/1.73 m(2) or serum creatinine (SCr) 0.8 to 1.1 mg/dL: give usual IV dose every 12 hours [13].
CrCl 10 to 25 mL/min/1.73 m(2) or SCr 1.2 to 1.5 mg/dL with decreasing urine output: give usual IV dose every 24 hours [13].
CrCl less than 10 mL/min/1.73 m(2) or SCr greater than 1.5 mg/dL or urine output less than 1 mL/kg/hour: decrease IV dose by 50% and give every 24 hours [13].

Uses

Neonatal herpes simplex virus (HSV) infections, known or suspected : Acyclovir treatment should be initiated in all infants, including HIV-positive, with herpes disease. In asymptomatic neonates born to women with active herpes lesions, initiation of acyclovir is dependent on risk of transmission to the neonate [6][4][5]. Adverse effects (AE) were common, but severe AEs were rare with a median dose of acyclovir 60 mg/kg/day IV in a retrospective review of Pediatrix Medical Group data (n=89 newborn infants) [18].

Dose Regimen

Based on results from a clinical trial, the standard dose and dosing interval is 20 mg/kg IV every 8 hours (60 mg/kg/day). Although mortality rate was reduced when compared with the 30 mg/kg/day (10 mg/kg/dose every 8 hours) regimen, the 60 mg/kg/day regimen still demonstrated a 24-month mortality rate of 31% among infants with disseminated HSV disease and 6% among infants with CNS HSV disease. Furthermore, the dose did not improve the rates of normal infant development [5][19]. Investigators of a small population pharmacokinetic study proposed the following frequencies for a 20 mg/kg dose: every 12 hours for infants less than 30 weeks postmenstrual age (PMA) (n=13), every 8 hours for infants 30 to less than 36 weeks PMA (n=9), and every 6 hours for infants 36 to 41 weeks PMA (n=6) to achieve a surrogate pharmacodynamic acyclovir target concentration of 3 mg/L or more. This target concentration theoretically would achieve CSF concentrations of 1 mg/L or more. Safety and efficacy were not evaluated with these regimens. One infant experienced an elevated serum creatinine, which was considered related to acyclovir. Doses greater than 80 mg/kg/day (range 87 to 158 mg/kg/day) were administered to 47% of neonates (15 out of 32 infants) [2].

Neonatal HSV infection, Chronic suppressive therapy

Based on data reported from 2 parallel, phase III, double-blind, placebo-controlled studies (n=45 with CNS disease; n=29 with skin, eye, mouth (SEM) disease), 6 months of suppressive oral acyclovir therapy (300 mg/m^2/dose 3 times a day) started immediately after IV treatment for CNS HSV disease was associated with better neurological outcomes when compared with placebo. Of the 28 infants with CNS disease assessed at 12 months (acyclovir=16; placebo=12), Bayley Scales of Infant Development (2nd Edition) Mental Scores were significantly higher in patients receiving acyclovir compared with patients receiving placebo (88.24 vs 68.12; p=0.046). In patients with SEM disease receiving 6 months of suppressive oral acyclovir therapy started immediately after IV treatment, the time to 2 recurrences of skin lesions was 1.7 months longer in the treatment group compared with placebo. Of the 15 infants with SEM disease assessed at 12 months, there were no differences in Bayley scores between acyclovir and placebo. An absolute neutrophil count of 500 cells/mm^3 or less was reported in 20% to 25% of patients receiving acyclovir compared with 5% to 7% receiving placebo; no patient had complications associated with neutropenia [7].

Varicella-zoster virus infections with CNS and pulmonary involvement. Acyclovir treatment is recommended in infants with varicella-zoster infection having CNS or pulmonary involvement [9][10][11][12].

Administration

Intravenous route: Administer as IV infusion over 1 hour at a concentration of 7 mg/mL or less in D_5W or NS [14].

Oral route: take with or without food; for suspension, shake well before measuring each dose [15].

Extravasation Management Neonatal data are limited to pooled data from 10 case reports/case series (n=237) and are not specific to acyclovir extravasation; subcutaneous saline irrigation with or without hyaluronidase infiltration was commonly used. No standardized management was established. An option for more severe injuries (stages 3 and 4) is subcutaneous irrigation with saline, but this is not advocated as standard treatment. Conservative management is appropriate for mild extravasation (stages 1 and 2) [16]. Although not neonatal-specific, the following are recommendations for extravasation of acidic or alkaline agents (acyclovir is alkaline with a pH of 11) [17]

- **General:**
- Stop and disconnect infusion; do not remove the cannula or needle
- Attempt to gently aspirate as much extravasated agent as possible; avoid manual pressure
- Remove cannula or needle
- Dry heat and elevation
- Closely monitor for signs of coagulation and ischemia
- Avoid attempt at pH neutralization (acyclovir - pH 11)
- Monitor and consider the need for surgical management such as surgical flushing with normal saline or debridement and excision of necrotic tissue (especially if pain persists for 1 to 2 weeks). In cases of compartment syndrome, surgical decompression may be required
- **Refractory Events:**
- Hyaluronidase 15 units intradermally along injection site and edematous area. Give as five, 0.2-mL intradermal injections along extravasation site and edematous tissue.
- **Inadvertent Intraarterial Administration:**
- Leave inadvertent intraarterial line in place for diagnostics
- Systemic heparin titrated to therapeutic anticoagulant effect.
- Stellate ganglion block

MEDICATION SAFETY

Contraindications/Precautions

Precautions

Administration: Rapid rate of infusion may lead to renal tubular damage [20]
Hematologic: Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome, including fatal cases, has been reported in immunocompromised patients [20].
Neurologic: Encephalopathic changes (eg, lethargy, obtundation, tremors, confusion, hallucinations, agitation, seizures, or coma) have been reported; use with caution in patients with underlying neurologic abnormalities, significant hypoxia, or serious renal, hepatic, or electrolyte abnormalities [20].
Renal: Impaired renal function may occur and is dependent upon rate of administration; risk is increased in patients with preexisting renal disease and dehydration, and with concomitant use of other nephrotoxic drugs [20].
Renal: Precipitation of acyclovir crystals in renal tubules may occur and can result in acute renal failure; accompany administration with adequate hydration [20].
Renal: Renal failure, including fatal cases, has been reported [20].

Adverse Effects

Common Adverse Effects: Common adverse events include nausea, vomiting, and rash [14].
Cardiovascular: Hypotension requiring inotropes (9%) occurred in a retrospective review of Pediatrix Medical Group data (n=89 newborn infants treated for herpes simplex virus disease) [18]
Hepatic: Elevations of hepatic transaminases (1% to 2%) [20].
Hematologic:
Leukopenia (16%) and thrombocytopenia (25%), which occurred within a median of 1 to 2 days, were common in a retrospective review of Pediatrix Medical Group data (n=89 newborn infants treated with high-dose acyclovir for herpes simplex virus disease). Neutropenia occurred in 6% of infants, most of whom were treated with granulocyte colony-stimulating factor. Severe hematologic events were rare (0% to 3%) [18].
Among infants receiving high-dose acyclovir for neonatal HSV disease, the major toxicity was neutropenia (absolute neutrophil count less than 1000/mm^3), which was observed in 20% of neonates [3]. Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome, resulting in death, have been reported in some immunocompromised patients receiving acyclovir. Overall, hematologic abnormalities occurred in less than 1% [20][14].
Immunologic: Development of certain acyclovir-resistant viruses may cause severe disease in infants [20].
Neurological: Seizures (9%) occurred in a retrospective review of Pediatrix Medical Group data (n=89 newborn infants treated with high-dose acyclovir for herpes simplex virus disease) [18]
Renal: Mild elevations of creatinine concentrations (2%) were reported in a retrospective review of Pediatrix Medical Group data (n=89 newborn infants treated with high-dose acyclovir for herpes simplex virus disease) [18]
Renal failure, in some cases fatal, has been reported [20]..
Vascular: Phlebitis at the injection site occurred in 9% of patients [20].

Solution Compatibility

D_5W and NS.

Terminal Injection Site Compatibility

Amikacin, ampicillin, aminophylline, cefazolin, cefotaxime, cefoxitin, ceftazidime, ceftriaxone, chloramphenicol, cimetidine, clindamycin, dexamethasone, erythromycin lactobionate, famotidine, fluconazole, gentamicin, heparin, hydrocortisone succinate, imipenem/cilastatin, linezolid, lorazepam, magnesium sulfate, metoclopramide, metronidazole, milrinone, morphine, nafcillin, oxacillin, penicillin G, pentobarbital, piperacillin, potassium chloride, propofol, ranitidine, remifentanil, sodium bicarbonate, theophylline, ticarcillin, tobramycin, trimethoprim/sulfamethoxazole, vancomycin, and zidovudine.

Terminal Injection Site Incompatibility

Fat emulsion. Aztreonam, caffeine citrate, caspofungin, cefepime, dobutamine, dopamine, meropenem, and piperacillin-tazobactam.

Monitoring

Laboratory
Monitor renal function at baseline and at least once weekly, particularly in patients with preexisting renal dysfunction on prolonged therapy [3].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Antiviral drug that is preferentially taken up by infected cells; inhibits viral DNA synthesis. CSF concentrations are 30% to 50% of serum concentrations. Oral absorption is 15% to 30%. Most of administered dose is excreted unchanged in urine, primarily via glomerular filtration. Protein binding and metabolism are minimal. Serum half-life is 3 to 4 hours in patients with normal renal and hepatic function.

The clearance increased with time in the premature neonate from 0.211 L/hr/kg for those less than 30 weeks postmenstrual age (PMA), 0.449 L/hr/kg for those 30 to less than 36 PMA, and 0.589 L/hr/kg for those 36 to 41 PMA in a population pharmacokinetic study

(n=28). The corresponding half-lives were 10.2 hours, 6.55 hours, and 3 hours. For 20 mg/kg doses, the IV frequency suggested was every 12 hours for infants less than 30 weeks PMA, every 8 hours for infants 30 to less than 36 weeks PMA, and every 6 hours for infants 36 to 41 weeks PMA. These regimens were then assessed using a data set of 1000 infants to simulate acyclovir exposure. The proposed dosing regimens predict that the steady state plasma concentration at 50% of the dosing interval would be greater than or equal to 3 mg/L in greater than 90% of infants. Although, toxic levels are unknown, concentrations associated with neurotoxicity in a small amount of patients have been identified as 50 to 70 mg/L. These predicted neurotoxic concentrations were exceeded in 0.9% and 0.3% of infants, respectively [2].
Dosing simulations of the proposed and standard dose regimens using a database of 1000 infants provide the following percentages of infants who would be expected to achieve a target concentration of 3 mg/L or more [2].

Regimens and Target Concentrations					
Postmenstrual Age	IV Dose	N	Percent of Infants with Concentrations of 3 mg/L or more		
			Cmax at steady state	C50 at steady state	Cmin at steady state
Proposed Regimen (Sampson, 2014)					
Less than 30 weeks	20 mg/kg/dose every 12 hours	218	100%	97%	89%
30 to less than 36 weeks	20 mg/kg/dose every 8 hours	373	98%	94%	75%
36 to 41 weeks	20 mg/kg/dose every 6 hours	409	96%	86%	56%
Standard Dose Regimen (Kimberlin, 2001)					
Less than 30 weeks	20 mg/kg/dose every 8 hours	218	100%	100%	100%
30 to less than 36 weeks	20 mg/kg/dose every 8 hours	373	98%	94%	74%
36 to 41 weeks	20 mg/kg/dose every 8 hours	409	94%	70%	10%
KEY: C50 at steady state = steady state plasma concentrations at 50% of the dosing interval					

Sampson, 2014

ABOUT

Special Considerations/Preparation

Injection
Availability: Solution (50 mg/mL) or as powder for solution in 500-mg and 1-g vials. Prepare powder for solution by dissolving contents of 500-mg vial in 10 mL sterile water for injection. Reconstituted solution is stable at room temperature for 12 hours. **Do not refrigerate**[14].

Infusion solution concentration should be no greater than 7 mg/mL[14].

A 5-mg/mL dilution may be made by adding 1 mL of 50 mg/mL concentration to 9 mL of preservative-free normal saline. Dilution should be used within 24 hours.

Oral
Oral suspension available in 200-mg/5 mL concentration. Store at room temperature. Shake well before administration [15].

Adenosine

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Paroxysmal Supraventricular Tachycardia (PSVT) Conversion
Initial dose: 50 to 100 mcg/kg (0.05 to 0.1 mg/kg) rapid IV push [1].
Repeat doses: If conversion of PSVT does not occur after 1 to 2 minutes, may repeat with doses increasing in increments of 50 to 100 mcg/kg/dose (0.05 to 0.1 mg/kg/dose) IV [1] every 1 to 2 minutes as needed; **maximum 0.3 mg/kg/dose or 12 mg/dose**[1].

Uses

Acute treatment of sustained paroxysmal supraventricular tachycardia.
It may also be useful in establishing the cause of the SVT.

Administration

Administer as a rapid IV bolus either centrally or peripherally. Infuse directly into a vein or as close to the patient as possible. Follow each dose with a rapid saline flush [1]. Intraosseous route is an option during resuscitation [2].

MEDICATION SAFETY

Contraindications/Precautions

Contraindicated in patients with second- or third-degree AV block and patients with sinus node disease, such as sick sinus syndrome or symptomatic bradycardia (except patients with functioning pacemaker) [3].

Cardiac arrest, in some cases fatal, sustained ventricular tachycardia (requiring resuscitation), and myocardial infarction have been reported following adenosine infusion. Patients with signs or symptoms of acute myocardial ischemia (eg, unstable angina or cardiovascular instability) have an increased risk for serious cardiovascular reactions with adenosine administration; therefore, avoid use in these patients. Cardiac resuscitative measures should be available prior to infusion [4].
Hemorrhagic and ischemic cerebrovascular accidents have been reported. Seizures (new or

recurrent) have been reported and may require emergent management. Concomitant use of aminophylline increases the risk of seizures [5].
Hypersensitivity reactions, including dyspnea, tightening of the throat, flushing, erythema, rash, and chest discomfort, have been reported and may require symptomatic treatment or resuscitative measures [6].

Adverse Effects

Flushing, dyspnea, and irritability occur frequently, but usually resolve within 1 minute. Transient (duration less than 1 minute) arrhythmias may occur between termination of SVT and onset of normal sinus rhythm. Apnea has been reported in one preterm infant. Recurrence of SVT occurs in approximately 30% of treated patients. Aminophylline/Theophylline and caffeine diminish adenosine's effect by competitive antagonism.

Solution Compatibility

D_5W and NS.

Monitoring

Continuous EKG and blood pressure monitoring.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Adenosine is the pharmacologically active metabolite of ATP. It acts by depressing sinus node automaticity and AV node conduction. It does **not** have negative inotropic effects. Response should occur within 2 minutes of the dose. Estimated serum half-life is 10 seconds.

ABOUT

Special Considerations/Preparation

Availability: 2-mL vials containing 6 mg (3 mg/mL) adenosine in NS. Contains no preservative.
Storage: Store at room temperature. **Do not refrigerate;** crystallization will occur. Solution must be clear at the time of use [1].
Dilutions can be made with NS for doses less than 0.2 mL (600 mcg). Use 1 mL (3000 mcg) with 9-mL NS to make a solution with a final concentration of 300 mcg/mL.

DOSING/ADMINISTRATION

Dose

Hemolytic disease of the newborn:
1 g/kg of 25% albumin IV administered approximately 1 hour prior to exchange transfusion [1][2].

Hypotension: 0.5 g/kg (10 mL/kg) of 5% albumin IV over 20 to 30 minutes; may be repeated [3][4][5][6] up to **maximum of 3 doses**[6].

Septic shock: 0.5 g/kg (10 mL/kg) of 5% albumin IV over 5 to 10 minutes with repeat doses as needed up to **maximum 3 g/kg (60 mL/kg)** in the first hour until perfusion improves or hepatomegaly develop [7].

Uses

Cardiopulmonary bypass, adjunct to priming fluids: The agents of choice for the priming solution for cardiopulmonary bypass pumps are crystalloid solutions (for example, lactated Ringer's solution and NS). Nonprotein colloids in addition to crystalloids may be preferred when pulmonary shunting is a concern. For postoperative volume expansion, the preferred order of choice is crystalloids, nonprotein colloids (for example hetastarch, dextran, and synthetic colloids), and lastly albumin [15].
In cardiopulmonary bypass performed in neonates, human albumin has been added to the priming solution [16][17][18].
In addition to other components, 5% albumin 200 mL replaced fresh frozen plasma [17] or 20% albumin 100 mL replaced a portion of the fresh frozen plasma in the priming solution [16].

Hemolytic disease of the newborn: Albumin may be used to bind free serum bilirubin in infants with severe hemolytic disease prior to exchange transfusion [1]; it should not be administered in conjunction with phototherapy [2]. Immunoglobulin, not albumin, is recommended in infants with isoimmune hemolytic disease and an increasing total serum bilirubin despite intensive phototherapy or when bilirubin is within 2-3 mg/dL of exchange level [19].

Hyperbilirubinemia, adjunct to exchange transfusion: Adjunctive albumin is not included in the American Academy of Pediatrics recommendations for management of hyperbilirubinemia, [19]. however, guidelines from the University HealthSystem Consortium state albumin may be considered as an adjunct to exchange transfusion if administered concurrently, and not before, transfusion [15].
At one institution, albumin is considered before exchange transfusion, especially if serum

albumin is less than 3.4 mg/dL [20]. Two studies of infants with intensive phototherapy failure (n=92; 32 weeks or more gestation; weighing more than 1000 g) demonstrated lower bilirubin levels at 6 and 12 hours post-exchange, shorter duration of phototherapy after exchange, and need for second exchange transfusion in albumin-treated neonates compared with the control group [21][22]. The dosing regimen was 1 g/kg IV of 5% [22] or 20% albumin [21] administered 1 to 2 hours prior to exchange.

Hyperbilirubinemia, adjunct to phototherapy: Adjunctive albumin is not included in the American Academy of Pediatrics recommendations for management of hyperbilirubinemia [19]. In addition, the University HealthSystem Consortium states that albumin should not be administered as an adjunct to phototherapy [15].
Human 25% albumin 1 g/kg IV during the first 2 hours of intensive phototherapy rapidly reduced (by 2 hours) unbound bilirubin values compared with no albumin in a retrospective study (n=58; gestational age 39.4 weeks; birthweight 3245 g) of Japanese infants with hyperbilirubinemia. However, there was no difference in total bilirubin values [23]. A follow-up study identified abnormalities of auditory brainstem responses at 6 months in 3 of 38 albumin-treated infants and 6 of 20 infants in the control group. At 2 years of age, abnormal development, including hearing loss, was not identified in either group [24].

Hypoalbuminemia: Albumin is not considered appropriate for treatment of hypoalbuminemia according to the University HealthSystem Consortium [15]. There is not enough evidence from randomized trials to determine if routine use of albumin (1 g/kg/day) in preterm neonates with hypoalbuminemia (less than 3 g/dL) is beneficial or harmful [25].

Hypotension: Albumin may be considered for volume expansion in neonates if 10 mL/kg of crystalloid solution is unsuccessful [15], however, the majority of very low birth weight (VLBW) premature infants (weighing 1500 grams or less and younger than 3 postnatal days) with hypotension are not hypovolemic [26][27]. When hypovolemia is present, albumin is generally not recommended for use; isotonic saline is preferred when a volume expander is needed [26].
Dopamine increased blood pressure better than albumin in preterm hypotensive neonates (weighing 1500 grams or less) younger than 24 hours (n=39) [28]. Albumin was superior to normal saline in neonates with hypotension in the first 24 hours of life in a randomized, double-blind study (n=101; mean birthweight 1528 to 1617 g; mean gestational age 30.1 to 30.8 weeks). Over 70% of neonates weighing less than 1500 g failed bolus therapy with either albumin or normal saline and required dopamine infusion. The rate for intraventricular hemorrhage was higher than the norm for both treatments; however, these hemorrhages were less common and less severe in the albumin treated group [3]. In contrast, 2 studies (n=104) did not demonstrate a difference between albumin and isotonic saline in normalizing mean arterial pressure [29][6].

Nephrotic syndrome, adjunct for edema: Diuretics alone are first line therapy, however, short-term use of 25% albumin may be considered in conjunction with a diuretic in patients with acute several peripheral or pulmonary edema having failure with diuretic therapy alone [15][30][15]. In pediatric patients with severe edema secondary to nephrotic syndrome, diuretics (eg, loop and thiazide) and 25% albumin infusions may be required in addition to a low-sodium diet and fluid restriction [31][15]. The benefit of albumin and a diuretic is transient and furthermore, albumin may lead to hypertension, pulmonary edema, and congestive heart failure [31].
Studies are lacking in neonates. In one case-series (n=7) of full-term infants diagnosed with

congenital nephrotic syndrome, the regimen was 20% albumin 1 g/kg IV (based upon ideal body weight) over 4 hours followed by IV furosemide (0.5 to 1 mg/kg) when needed [32].

Perioperative hemodynamic support: No differences in hemodynamics, fluid input, or fluid output were observed between perioperatively administered human 5% albumin and 6% hydroxyethyl starch 130/0.4 (Voluven®) in newborns (at 30 weeks gestation) and infants younger than 24 months of age undergoing non-cardiac surgery in a randomized, open-label trial (n=82). Infusion volume and rate were adjusted to maintain stable hemodynamics [33].

Polycythemia, adjunct to dilutional exchange transfusion: Crystalloid solutions, such as normal saline or Ringers solution, are considered the solutions of choice for exchange transfusion in neonates with polycythemia. Albumin is more expensive, frequently in short supply, and has a potential risk of infection. [34][35].

Resuscitation: Albumin is not used during neonatal resuscitation. Isotonic crystalloid solution or blood is recommended for volume expansion during resuscitation [36].

Severe Sepsis and Septic Shock:[7][37]

<table>
<tr><td colspan="3">Hemodynamic Support - First 60 Minutes</td></tr>
<tr><td>Time</td><td colspan="2">Management- Proceed to next step if shock persists</td></tr>
<tr><td>0 minutes</td><td colspan="2">Maintain airway and establish access</td></tr>
<tr><td>5 minutes</td><td colspan="2">Push 10 mL/kg isotonic crystalloid or colloid boluses up to 40 mL/kg until improved perfusion or unless hepatomegaly.
Begin prostaglandin infusion until rule out ductal-dependent lesion.</td></tr>
<tr><td rowspan="2">15 minutes</td><td colspan="2">DOPamine less than 10 mcg/kg/min +/- DOBUTamine for fluid-refractory shock</td></tr>
<tr><td colspan="2">EPINEPHrine 0.05 to 0.3 mcg/kg/min for fluid-refractory DOPamine-resistant shock</td></tr>
<tr><td rowspan="2">60 min</td><td>Cold shock-Poor LV function
Normal blood pressure
ScvO(2) less than 70%*/Hgb greater than 12 g/dL
SVC flow less than 40 mL/kg/min or CI less than 3.3 L/min/m(2)</td><td>Add nitrovasodilator milrinone or inamrinone with volume loading</td></tr>
<tr><td>Cold shock- Poor RV function
PPHN
ScvO(2) less than</td><td>Inhaled nitric oxide
Inhaled iloprost or IV adenosine
IV milrinone or</td></tr>
</table>

	70%* SVC flow less than 40 mL/kg/min or CI less than 3.3 L/min/m(2)	inamrinone
	Warm shock- Low blood pressure	Titrate volume Add norepinephrine Vasopressin or terlipressin or angiotensin
	Refractory shock	Hydrocortisone if absolute adrenal insufficiency. Triiodothyronine if hypothyroid. Begin pentoxifylline if VLBW newborn. Consider closing PDA if hemodynamically significant.
	ECMO	
Goals •First Hour: restore and maintain heart rate thresholds, capillary refill of 2 seconds or less, and normal blood pressure. • NICU: normal MAP-CVP, preductal and postductal oxygen saturation difference less than 5%, *ScvO(2) greater than 70% (except congenital heart patients with mixing lesions), SVC flow greater than 40 mL/kg/min, or cardiac index greater than 3.3 L/min/m(2)		
KEY: CI = cardiac index, Hgb = hemoglobin, LV function = left ventricle function, MAP-CVP = mean arterial pressure-central venous pressure, PDA = patent ductus arteriosus, PPHN = persistent pulmonary hypertension of the newborn, ScvO(2) = continuous central venous oxygen saturation, SVC = superior vena cava, VLBW = very low birth weight		
Davis et al: Crit Care Med 2017;45(6)		

Pediatric FDA Approved Indications

AlbuRx®-25 and Flexbumin® 25%: Indicated for hemolytic disease of the newborn to attempt to bind and detoxify unconjugated bilirubin in infants with severe hemolytic disease prior to exchange transfusion [1][2].

Kedbumin™: In patients 12 to 16 years of age, indicated for hypovolemia, hypoalbuminemia, burns (after 24 hours post burn in patients experiencing severe albumin depletion in order to favor edema reabsorption), ovarian hyperstimulation syndrome, and adult respiratory distress syndrome, and in cardiopulmonary bypass (as part of the priming fluids), hemodialysis, and to prevent central volume depletion after paracentesis due to

cirrhotic ascites [14].
Safety of albumin solutions has been demonstrated in children provided the dose is appropriate for body weight; however, the safety of Flexbumin® 25% has not been evaluated in sponsor conducted pediatric studies[1]. No clinical studies using Albuminar®-5 have been conducted in pediatric patients. Safety and effectiveness in pediatric patients have not been established. However, extensive experience in patients suggests that children respond to Albuminar®-5 in the same manner as adults [8]

Administration

•Administer slow enough to avoid too-rapid plasma volume expansion. The 5% and 25% may be administered without dilution or diluted with normal saline or D5W [1][8]. Adequately hydrate patients during or after infusion of albumin 25% solutions [9][10].
•In patients with normal blood volume, avoid circulatory overload and pulmonary edema by administering albumin no faster than 1 mL/min [1][11][12].
•In the presence of hypertension, infuse at a slower rate [13][8].
•Do not administer more than 4 hours after vial has been entered. Ensure substitution of other blood constituents (coagulation factors, electrolytes, platelets, and erythrocytes) is adequate when replacing comparatively large volumes of albumin or if blood loss is severe [1][9][14][2].

•Warm to room temperature if infusing large volumes. In plasma exchange, adjust infusion rate to the rate of removal [14].

MEDICATION SAFETY

Contraindications/Precautions

Contraindicated :
•Severe anemia or cardiac failure [14][38][9][10] with normal or increased intravascular volume
•History of hypersensitivity reaction to albumin preparations or to any component of the product (eg, N-acetyltryptophan, sodium caprylate) [11][1]

Precaution
Administration: Conditions where hypervolemia and/or hemodilution may occur may require dose and infusion rate adjustment; increased risk with heart failure, hypertension, esophageal varices, pulmonary edema, hemorrhagic diathesis, severe anemia, and renal failure; monitoring recommended [11][1]
Administration: Circulatory overload or cardiac overload (eg, headache, dyspnea, jugular venous distention, rales and abnormal elevations in systemic or central venous blood pressure) may occur; monitoring recommended [11][1][39][40][41]; discontinue use at first clinical signs of cardiovascular overload [11][1]
Administration: Rapid rise in blood pressure may occur; monitoring recommended

[39][40][41]
Administration: Do not dilute product with Sterile Water for Injection as there is risk of hemolysis, including potentially fatal cases, and acute renal failure in recipients [11][1]
Hematologic: Re-bleeding secondary to clot disruption can occur in trama and postoperative surgery patients; monitoring recommended [11][1]
Immunologic: Hypersensitivity reactions, including anaphylactic reactions, have been observed; discontinue use for suspected hypersensitivity reaction; implement standard treatment for anaphylactic shock [11][1]
Immunologic: Infectious agent transmission may occur, including a risk of exposure to viruses, Creutzfeldt-Jakob disease or variant Creutzfeldt-Jakob disease, and other pathogens [11][1][39][40][41].

Adverse Effects

Common: flushing, urticaria, fever, chills, nausea, vomiting, tachycardia, and hypotension. These reactions usually subside when the infusion rate is slowed or stopped [14].

Lid edema occurred in 19.5% and 29.3% of newborns (at 30 weeks gestation) and infants younger than 24 months of age undergoing non-cardiac surgery receiving albumin 5% and hydroxyethyl starch 130/0.4, respectively [33].

Solution Compatibility

D_5W, $D_{10}W$, D_5LR, D_5NS, $D_50.45\%NaCl$, NS, 0.45%NaCl.

Solution Incompatibility

Protein hydrolysates, amino acid mixtures, or alcohol-containing solutions [2][14].

Terminal Injection Site Compatibility

Albumin, Human, 20%
Lorazepam 0.33 mg/mL.

Albumin, Human, 25%
Diltiazem 5 mg/mL, ketamine 50 mg/mL.

Terminal Injection Site Incompatibility

Fat emulsion, micafungin, midazolam, vancomycin, verapamil.

Monitoring

Closely monitor infusion rates and the patient's clinical state during infusion. Observe injured patients after restoration of blood pressure for bleeding points that may have failed to bleed at lower blood pressure [38][9][10].

Closely monitor for circulatory overload during administration. Regularly monitor hemodynamic performance, including arterial blood pressure and pulse rate, central venous pressure, pulmonary artery occlusion pressure, urine output, electrolyte levels, and HCT/Hb [14].
Closely monitor hemodynamic parameters after administering for evidence of cardiac or respiratory failure, renal failure or increasing intracranial pressure [11][1]

For a full-term newborn, the target heart rate and perfusion pressure (mean arterial pressure minus central venous pressure) are 110 to 160 beats/min and 55 mmHg, respectively [7].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Albumin products of various concentration are an aqueous solution of albumin obtained from large pools of human plasma. The colloid osmotic or oncotic properties of albumin are utilized for plasma or blood volume deficit and for oncotic deficit from hypoproteinemia [10][38][9][2].[14]. Albumin's ability to bind and transport various molecules allows for use to bind free albumin in infants having severe hemolytic disease of the newborn [2].
The total exchangeable albumin pool is 4 to 5 g/kg (intravascular, 40% to 45%; extravascular, 55% to 60%) and the half-life of albumin is approximately 19 days. Metabolism is achieved by feedback regulation; elimination is primarily intracellular (lysosomal proteases). During the first 2 hours following albumin infusion in healthy subjects, less than 10% leaves the intravascular compartment [14].

ABOUT

Special Considerations/Preparation

Albuminar®-5: Preservative-free IV solution containing serum albumin 5% and supplied as

2.5 g/50 mL, 12.5 g/250 mL, and 25 g/500 mL in single-dose vials. May be administered undiluted [10].

Albuminar®-20: Preservative-free IV solution containing serum albumin 20% and supplied as 10 g/50 mL and 20 g/100 mL in single-dose vials [38].

Albuminar®-25: Preservative-free IV solution containing serum albumin 25% and supplied as 5 g/20 mL, 12.5 g/50 mL, and 25 g/100 mL in single-dose vials [9].

AlbuRx®-25: Preservative-free IV solution containing serum albumin 25% and supplied as 12.5 g/50 mL and 25 g/100 mL in single-dose vials. Do not store at temperatures above 30 degrees C (86 degrees F) [2].

Flexbumin® 5%: Preservative-free IV solution containing serum albumin 25% and supplied as 12.5 g/250 mL in a single-dose plastic container. Do not store above 30 degrees C and protect from freezing [1]

Flexbumin® 25%: Preservative-free IV solution containing serum albumin 25% and supplied as 12.5 g/50 mL and 25 g/100 mL in single-dose plastic containers. Do not store above 30 degrees C and protect from freezing [1]

Kedbumin™: Preservative-free IV solution containing serum albumin 25% (0.25 g/mL) and supplied in 50-mL and 100-mL single-dose vials. Do not freeze or store above 30 degrees C. Protect from light [14].

Albumin 25% solutions should only be diluted in suitable infusion solutions, such as D_5W or NS. Dilution of albumin 25% with sterile water for injection produces a hypotonic solution that may result in life-threatening hemolysis and acute renal failure [1][9][14][2].

DOSING/ADMINISTRATION

Dose

Bronchodilation: 0.1 to 0.5 mg/kg/dose every 2 to 6 hours via nebulizer.
1 Metered-dose inhaler (MDI) actuation per dose (approximately 0.1 mg or 100 mcg) every 2 to 6 hours via MDI with spacer device placed in the inspiratory limb of the ventilator circuit. Simulated neonatal lung models suggest greater delivery when using a spacer with the MDI. Use chlorofluorocarbon free preparations when administering to neonates.
For nebulizations, use preservative-free solutions; benzalkonium chloride in the 20-mL multidose bottles may cause bronchoconstriction, particularly with frequent or continuous administration [1].

Oral: 0.1 to 0.3 mg/kg/dose orally every 6 to 8 hours.

Treatment of hyperkalemia
Preterm neonates: 0.4 mg/dose every 2 hours via nebulization until serum potassium decreases to desired safe level (eg, less than 5 mmol/L) [2]. Consider alternative potassium-lowering therapies for potassium levels greater than 7.5 mmol/L.
Neonates (AAP guidelines): 2.5 mg/dose via nebulization. If using intermittent nebulizer treatment with 0.5% mL solution, may administer every 20 mins for 1 to 2 doses [3]

Uses

Bronchodilator
Hyperkalemia in preterm neonates: Published data using the nebulized formulation of albuterol for the treatment of hyperkalemia in preterm neonates are limited to one randomized, placebo-controlled trial (n=19). Following administration every 2 hours until serum potassium dropped below 5 mmol/L (or a maximum of 12 doses), nebulized albuterol (n=8) was effective in lowering potassium levels at 4 and 8 hours when compared with placebo (saline via nebulization; n=11) [2].

Bronchiolitis: Albuterol is not recommended for the routine treatment of bronchiolitis in infants and children. Consistent benefits have not been demonstrated. There are a lack of data in those with severe disease or with respiratory failure [13].

Administration

Inhalation

ProAir® HFA, Proventil® HFA, Ventolin® HFA
Metered-dose inhaler: Shake well before each spray; canister should be at room temperature before use. Prime before using for the first time, or if the inhaler has not been used for more than 2 weeks, or when the inhaler has been dropped; prime the inhaler by spraying it 4 times for Proventil® HFA or Ventolin® HFA or 3 times for ProAir® HFA into the air, away from the face [4][5][6]. Use a spacer or a valve holding chamber in younger patients (less than 5 years of age) or patients with poor inhaler technique. A mask should be added for children less than 4 years of age [7].
Proair® Respiclick™, Proair® Digihaler™
Metered-dose inhaler: Does not require priming [8][9]
Do not use with spacer or volume holding chamber [8][9]
Keep inhaler clean and dry by wiping with dry cloth or tissue as needed; never wash or put any part of inhaler in water [8][9]

Nebulization
Solution for inhalation: Use the entire contents of pre-diluted vials for inhalation via nebulizer immediately after opening [10]. The dose withdrawn from the 0.5% 20-mL multidose bottle must be further diluted with sterile normal saline to a total volume of 3 mL prior to administration [11]. Preservative-free solutions are recommended, particularly with continuous nebulization; benzalkonium chloride in 20-mL multidose bottles may cause bronchoconstriction [1]. There are no data in neonates, however, no significant differences in response were observed between albuterol solutions with and without benzalkonium chloride in a retrospective study of 128 hospitalized pediatric patients (4 to 17 years of age) administered continuous nebulized albuterol [12].
Administer via nebulizer over 5 to 15 minutes at a gas flow of 6 to 8 L/minute [11][7][10]. A tight-fitting face mask should be used in patients who cannot use a mouthpiece [7].

MEDICATION SAFETY

Contraindications/Precautions

Contraindications
Proair® Respiclick™ and Proair® Digihaler™ are **contraindicated** in patients with history of hypersensitivity to albuterol and/or severe hypersensitivity to **milk proteins** [8][9].

Precautions
Cardiovascular: Use sympathomimetic amines with caution in patients with preexisting cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; possibility for cardiovascular events seen in heart rate, blood pressure and ECG changes [8][9][6][14][15][16][17][18]. Discontinuation may be required [8][9]
Cardiovascular: Avoid use for the treatment of hyperkalemia in patients with preexisting cardiac arrythmia (AAP guidelines) [3]
Endocrine and metabolic: Use caution in patients with preexisting diabetes mellitus [8][9] [6][15][14][16][17][18] as large doses of IV albuterol have been reported to aggravate condition [8][9]
Endocrine and metabolic: Use caution in patients with preexisting ketoacidosis [8][6]

[15][14] as large doses of IV albuterol have been reported to aggravate condition [8][9]
Endocrine and metabolic: Use caution in patients with preexisting hyperthyroidism [8][9][6][14][15][16][17][18]
Endocrine and metabolic: Hypokalemia has occurred but considered transient and not requiring supplementation, but has potential to lead to other cardiovascular side effects [8][9][6][14][15][16][17][18]
Higher doses: Fatalities have been reported upon exceeding recommended doses or excessive use. The cause of death is unknown, but severe acute asthmatic crisis and subsequent hypoxia suspected [8][9][6][15][14]
Immunologic: Rare immediate hypersensitivity can occur and manifest as symptoms of urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema [8][9]. Consider not reinitiating if immediate hypersensitivity occurs [8][6][15][14]
Immunologic: Lactose, used as an inactive ingredient in some inhalers, could lead to immediate hypersensitivity reactions to milk proteins, including anaphylaxis, angioedema, pruritus, and rash [8][9]
Neurologic: Use caution in patients with preexisting convulsive disorders [8][9][6][15][14][16][17][18]
Respiratory: Beta adrenergic agonist therapy alone may be insufficient to control asthma in many patients; consider adding anti-inflammatory agents (eg, corticosteroids) to therapeutic regimen [8]
Respiratory: Benzalkonium chloride preservative, in the multi-dose bottle for nebulization, may induce bronchoconstriction; use only single-use preservative-free, albuterol, particularly when using continuous nebulized albuterol (off-label use) [1].
Respiratory: Asthma deterioration may occur suddenly over a few hours or chronically over a few days; use of more albuterol than usual may indicate asthma deterioration [9], consider alternative therapy [6][15][14] and reevaluation of treatment regimen, giving special consideration to possible need for anti-inflammatory treatment [8]
Respiratory: Potentially life-threatening paradoxical bronchospasm has been reported and often occurs with first use of new canister. Discontinue immediately if this occurs and consider alternative treatments [8][9][6][15][14]

Adverse Effects

Tachycardia, arrhythmias, tremor, hypokalemia, and irritable behavior.

Monitoring

Therapeutic Laboratory Monitoring

Assess degree of bronchospasm and monitor serum potassium [2].
Hyperkalemia: Monitor serum potassium. The expected decrease within an hour of administration of albuterol is 1 to 1.5 mEq/L [3]

Toxic Laboratory Monitoring

Continuous EKG monitoring. **Consider not administering when heart rate is greater than 180 beats per minute.** Serum potassium [2].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Specific β_2-adrenergic agonist. Minimal cardiovascular effects unless used concurrently with aminophylline. Stimulates production of intracellular cyclic AMP, enhancing the binding of intracellular calcium to the cell membrane and endoplasmic reticulum, resulting in bronchodilation. Enhances mucociliary clearance. Drives potassium intracellular. Studies in vitro indicate that approximately 5% of a MDI dose administered using an in-line holding chamber/spacer device, versus less than 1% of a nebulizer dose, is delivered to the lung. Optimal aerosol dose in neonates is uncertain due to differences in aerosol drug delivery techniques. The therapeutic margin appears to be wide.
Well absorbed when administered orally. Onset of action is 30 minutes; duration is 4 to 8 hours. Serum half-life is approximately 6 hours (adults). Time to peak serum concentration is 3 to 4 hours. Tolerance may develop.

ABOUT

Special Considerations/Preparation

Oral dosage form: Syrup, 2 mg/5 mL.

Solution for inhalation: Pre-diluted 0.63 mg/3 mL (0.021%), 1.25 mg/3 mL (0.042%), and 2.5 mg/3 mL (0.083%) unit dosed vials. Albuterol 0.5% multidose 20-mL bottle contains benzalkonium chloride 0.01%. After the dose is withdrawn from the concentrated 0.5% solution, dilute with sterile normal saline to a total volume of 3 mL per dose prior to nebulization [11].
Store unit dose vial in protective foil pouch at all times to protect it from light; use within 1 week once removed from the foil pouch. Do not use if the solution in the vial changes color or becomes cloudy. Store at controlled room temperature between 20 to 25 degrees C [19][10].
Stability and Sterility
Preservative-free (PF) Albuterol Solution (0.67 mg/mL and 0.17 mg/mL): Albuterol single-use mini nebs (2.5 mg/0.5 mL, PF, Nephron Pharmaceuticals, West Colombia, SC) diluted with normal saline for irrigation to a concentration of 0.67 mg/mL and 0.17 mg/mL was stable through 168 hours when stored at room temperature (20 to 25°C) and at refrigeration (2 to 8°C). There was no bacterial growth detected throughout 10 days of incubation. [20].
Stability and Sterility
Benzalkonium Chloride (BAC)-Albuterol Solution (0.67 mg/mL and 0.17 mg/mL): Albuterol BAC (5 mg/mL, Hi-Tech Pharmaceuticals, Amityville, NY) diluted with normal saline for irrigation to a concentration of 0.67 mg/mL and 0.17 mg/mL was stable through 168

hours when stored at room temperature (20 to 25°C) and at refrigeration (2 to 8°C). There was no bacterial growth detected throughout 10 days of incubation. [20].

Metered-Dose Inhaler: Pressurized hydrofluoroalkane metered dose inhaler (contains no chlorofluorocarbons (CFC)). Proventil® HFA and Ventolin® HFA 90 mcg albuterol base per actuation.

Alprostadil

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Initial dose: 0.05 to 0.1 mcg/kg per minute by continuous IV infusion.
Titrate to infant's response--oxygenation *versus* adverse effects.

Maintenance dose: May be as low as 0.01 mcg/kg per minute.
Higher initial doses are usually no more effective and have a high incidence of adverse effects.
May also be given via UAC positioned near ductus arteriosus.

Uses

To promote **dilation of ductus arteriosus** in infants with congenital heart disease dependent on ductal shunting for oxygenation/perfusion.

Pediatric FDA Approved Indications
To promote dilation of ductus arteriosus in infants with congenital heart disease (ie, pulmonary atresia, pulmonary stenosis, tricuspid atresia, tetralogy of Fallot, interruption of the aortic arch, coarctation of the aorta, or transposition of the great vessels with or without other defects) dependent on ductal shunting for oxygenation/perfusion [1][3][4][5]. Low success rates for prostaglandin E_1 are usually due to an irreversibly closed ductus and severe acidemia and collapse. Functional closure of the ductus occurs within a few hours of birth, and anatomical closure occurs in 21 days (normal term infant) [4].

Administration

Continuous infusion via a large vein is the preferred route of administration. May also be given via UAC positioned near the ductus arteriosus. For continuous infusion, dilute in compatible solution to a concentration of 2 to 20 mcg/mL [1]. The recommended standard concentrations are 1, 2.5, 5, 10, and 20 mcg/mL for continuous infusions [2].

MEDICATION SAFETY

Contraindications/Precautions

CONTRAINDICATIONS: None

PRECAUTIONS:
Cardiovascular: Structural alterations (intimal lacerations, decreased medial muscularity, and disruption of the medial and internal elastic lamina) of the ductus and pulmonary arteries have been observed [6].
Gastrointestinal: Gastric outlet obstruction due to antral hyperplasia may occur; dose- and duration-related [6].
Hematological: Use with caution in neonates with bleeding tendencies [6].
Musculoskeletal: Cortical proliferation of the long bones has been observed with long-term infusions; resolution with discontinuation of alprostadil [6].
Respiratory: Do not use in neonates with respiratory distress syndrome [6].

Adverse Effects

Common (6% to 15%): Apnea (consider treating with aminophylline), hypotension, fever, leukocytosis, cutaneous flushing, and bradycardia. Hypokalemia reported with long-term therapy (greater than 20 days), especially with doses greater than 0.05 mcg/kg/minute. Gastric outlet obstruction and reversible cortical proliferation of the long bones after prolonged treatment (greater than 120 hours).

Uncommon (1% to 5%): Seizures, hypoventilation, tachycardia, cardiac arrest, edema, sepsis, diarrhea, and disseminated intravascular coagulation.

Rare (less than 1%): Urticaria, bronchospasm, hemorrhage, hypoglycemia, and hypocalcemia.
Musculoskeletal changes: Widened fontanels, pretibial and soft tissue swelling, and swelling of the extremities may occur after 9 days of therapy. Cortical hyperostosis and periostitis may occur with long-term (greater than 3 months) therapy. These changes resolve over weeks after discontinuation of therapy.

Black Box Warning

Apnea has been reported in 10% to 12% of neonates with congenital heart defects treated with alprostadil. Apnea is seen most often in neonates weighing less than 2 kg at birth, and usually appears during the first hour of drug infusion. Monitor respiratory status throughout treatment and be prepared to intubate/resuscitate.

Solution Compatibility

D_5W and NS.

Terminal Injection Site Compatibility

Aminophylline, ampicillin, caffeine citrate, calcium chloride, cefazolin, cefotaxime, cimetidine, clindamycin, dobutamine, dopamine, fentanyl, furosemide, gentamicin, glycopyrrolate, metoclopramide, metronidazole, nitroglycerin, nitroprusside, potassium chloride, penicillin G, tobramycin, vancomycin, and vecuronium.

Monitoring

Therapeutic
Restricted pulmonary blood flow: Improvement in blood oxygenation demonstrates efficacy [6]
Restricted systemic blood flow: Improvement of systemic blood pressure and blood pH demonstrates efficacy [6]

Toxic
Cardiovascular: Measure arterial pressure intermittently by umbilical artery catheter, auscultation, or with a Doppler transducer [6].

Gastrointestinal: Monitor for signs and symptoms of antral hyperplasia and gastric outlet obstruction in neonates administered alprostadil for more than 120 hours [6].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Alprostadil causes vasodilation of **all** arterioles. Inhibition of platelet aggregation. Stimulation of uterine and intestinal smooth muscle. Maximal drug effect usually seen within 30 minutes in cyanotic lesion; may take several hours in acyanotic lesions.

ABOUT

Special Considerations/Preparation

Supplied: 500 mcg in 1 mL of dehydrated alcohol ampules that must be refrigerated. **Dilute before administration to a concentration of 20 mcg/mL or less.** Prepare fresh infusion solutions every 24 hours.

Dilutions and Stability

Alprostadil 11 mcg/mL in 250 mL of 0.9% sodium chloride stored in polyvinyl chloride (Viaflex) containers at refrigerated temperature and protected from light was stable for 10 days. Prostin VR Pediatric® was used for this stability study [7].

Alprostadil 20 mcg/mL in 0.9% sodium chloride stored in glass ampules or plastic syringes was stable (degrades to 90%) for 106.5 days at 4°C and 9.8 days at 25°C and stable (degrades to 95%) for 51.8 days at 4°C and 4.8 days at 25°C. Storage in plastic syringes led to components leaching from the plastic and silicone piston head seals. Prostin VR Pediatric® was used for this stability study [8].

When mixing in a volumetric infusion chamber, undiluted alprostadil should not come in contact with the walls of the chamber. Add the appropriate amount of IV solution to chamber, then add the undiluted alprostadil solution. Replace volumetric infusion chamber if the appearance of the chamber changes and the solution becomes hazy[6].

Sample Dilution and Infusion Rate: Mix 1 ampule (500 mcg) in 50 mL of compatible solution (eg, D_5W) yielding an approximate concentration of 10 mcg/mL. Infuse at a rate of 0.01 mL/kg/min to provide a dose of 0.1 mcg/kg/minute [6]

DOSING/ADMINISTRATION

Dose

Restoration of function to central venous catheter: Instill into dysfunctional catheter at a concentration of 1 mg/mL. Use 110% of the internal lumen volume of the catheter, not to exceed 2 mg in 2 mL. If catheter function is not restored in 120 minutes after 1 dose, a second dose may be instilled.
An alternative dosing regimen using a smaller dose (0.5 mg diluted in NS to volume required to fill the central venous catheter) was used in children 10 kg or less in 1 study (n=25; infants as young as 7 weeks included).

Dissolution of intravascular thrombi: 200 mcg/kg per hour (0.2 mg/kg per hour). Duration of therapy is 6 to 48 hours. If administering directly into the thrombus, dose may be increased after 6 hours to a maximum of 500 mcg/kg per hour. If localized bleeding occurs, stop infusion for 1 hour and restart using 100 mcg/kg per hour. Discontinue heparin several hours prior to initiation of therapy.

Note: Reports in the literature are a collection of cases gathered over several years. Some authors used loading doses, others did not. Infused doses ranged from 20 to 500 mcg/kg per hour. Complications were most often linked with higher doses and longer duration of therapy. Call 1-800-NOCLOTS for case reporting and treatment guidance.

Uses

Dissolution of intravascular thrombi of recent onset that are either intraarterial or life-threatening. Adjuvant treatment of infective endocarditis vegetations.

Restoration of function to central venous access devices as assessed by the ability to withdraw blood.

Administration

Restoration of function to central venous catheter: Concentration of 1 mg/mL. Use 110% of the internal lumen volume of the catheter, not to exceed 2 mg in 2 mL [1][2][3][4]. Alternatively, use a smaller dose (0.5 mg diluted in NS to volume required to fill the central venous catheter) [5].

Dissolution of intravascular thrombi: May be administered as reconstituted at 1 mg/mL

or further diluted in compatible diluent (in PVC bags or glass vials) to a concentration of 0.5 mg/mL [6].

Call 1-800-NOCLOTS for case reporting and treatment guidance.

MEDICATION SAFETY

Contraindications/Precautions

Use is **contraindicated** in patients with acute ischemic stroke under the following conditions [7]:

- Active internal bleeding
- Bleeding diathesis
- Current intracranial hemorrhage
- Hypertension that is current, severe, and uncontrolled
- Intracranial or intraspinal surgery within the last 3 months
- Intracranial conditions that may increase the risk of bleeding (ie, neoplasm, aneurysm, arteriovenous malformation)
- Serious head trauma within the last 3 months
- Subarachnoid hemorrhage

Use is **contraindicated** for the treatment of acute myocardial infarction or pulmonary embolism under the following conditions [7]:

- Active internal bleeding
- Bleeding diathesis
- Hypertension that is current, severe, and uncontrolled
- Intracranial or intraspinal surgery within the last 3 months
- Intracranial conditions that may increase the risk of bleeding (ie, neoplasm, aneurysm, arteriovenous malformation)
- Recent history of stroke
- Serious head trauma within the last 3 months

Precautions

Administration: Avoid noncompressible arterial, internal jugular, or subclavian punctures or IM injection [7]

Angioedema: Angioedema has been reported during and up to 2 hours after administration in patients with ischemic stroke or myocardial infarction; risk may have been increased with use of concomitant ACE inhibitors. Discontinue and institute appropriate therapy if condition occurs [8]

Cardiovascular: Acute pericarditis or subacute bacterial endocarditis increase the risk of adverse effects [7]
Cardiovascular: Increased risk of thromboembolic events in patients with high likelihood of left-heart thrombus (eg, mitral stenosis or atrial fibrillation) [8]
Cardiovascular: Hypertensive patients (systolic, 175 mmHg or greater; diastolic, 110 mmHg or greater) are at an increased risk of adverse effects [7]
Cardiovascular: Stroke risk may outweigh treatment benefit in myocardial infarction patients at low risk of cardiac death [7]
Endocrine and metabolic: Cholesterol embolism has been reported with thrombolytic agents [7]
Gastrointestinal: Recent gastrointestinal bleeding increases the risk of alteplase adverse effects [7]
Hematologic: Fatal hemorrhage associated with traumatic intubation has occurred [7]
Hematologic: If treatment is initiated before coagulation test results are available, discontinue if baseline INR or aPTT elevations are seen [7]
Hematologic: Bleeding may occur with concurrent anticoagulant therapy, especially at arterial puncture sites. If serious bleeding develops, discontinue and treat appropriately [8]
Hematologic: Active internal bleeding or embolic complications may occur with venous catheter occlusion [2]
Hematologic: Significant or fatal internal (ie, intracranial, retroperitoneal, gastrointestinal, genitourinary, respiratory) or external bleeding have been reported; discontinue use if serious bleeding occurs [9]
Hematologic: Serious bleeding at critical location can occur; discontinue use [2]
Hematologic: Septic thrombophlebitis increases the risk of adverse effects [7]
Hematologic: An occluded AV cannula at a seriously infected site increases the risk of adverse effects [7]
Hematologic: Hemostatic defects, including defects secondary to severe renal or hepatic disease, increase the risk of adverse effects [7]
Hematologic: Underlying DVT may not be adequately treated in pulmonary embolism patients [8]
Hematologic: Increased risk of re-embolization due to lysis of underlying DVT in pulmonary embolism patients [8]
Hematologic: Minimize arterial and venous punctures due to an increased risk of bleeding; discontinue use if serious bleeding occurs [7]
Hematologic: Thrombocytopenia [2]
Hepatic: Significant hepatic dysfunction increases the risk of adverse effects [7]
Immunologic: Hypersensitivity, including urticarial and anaphylactic reactions (eg, laryngeal edema, rash, and shock) with rare fatal outcome, have been reported [8][10]; if hypersensitivity occurs, discontinue use and institute appropriate therapy [8]
Immunologic: Catheter infection may occur with venous catheter occlusion [2]
Neurologic: Cerebrovascular disease increases the risk of adverse effects [7]
Ophthalmic: Hemorrhagic ophthalmic conditions, including diabetic hemorrhagic retinopathy, increase the risk of adverse effects [7]
Renal: Recent genitourinary bleeding increases the risk of adverse effects [7]
Reproductive: Pregnancy may increase the risk of adverse effects [7]
Reproductive: Recent genitourinary bleeding may increase the risk of adverse effects [7]
Surgery: Recent major surgery increases the risk of adverse effects [7][2]
Special populations: Recent trauma increases the risk of adverse effects [7]

Adverse Effects

Intracranial hemorrhage may occur, especially in premature infants treated for prolonged periods. Bleeding from venipuncture sites occurs in approximately half of treated patients. The risk of complications increases at doses above 450 mcg/kg per hour.

Solution Compatibility

NS and D_5W.

Terminal Injection Site Compatibility

Lidocaine, morphine, nitroglycerin, and propranolol.

Terminal Injection Site Incompatibility

Dobutamine, dopamine, and heparin.

Monitoring

Follow coagulation studies (PT, aPTT, fibrinogen, fibrin split products) prior to therapy and at least daily during treatment. Maintain fibrinogen levels greater than 100 mg/dL and platelets greater than 50,000/mm^3. Echocardiography to assess clot lysis at least every 12 hours (every 6 hours optimal). Cranial ultrasound to assess for hemorrhage prior to therapy.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Alteplase binds strongly and specifically to fibrin in a thrombus and converts the entrapped plasminogen to plasmin. This initiates local fibrinolysis with limited systemic proteolysis. Alteplase has a shorter half-life than streptokinase and does not cause anaphylactic reactions. It is cleared rapidly from the plasma, primarily via the liver.

ABOUT

Special Considerations/Preparation

Activase® is supplied as lyophilized powder in 50 mg and 100 mg vials. Reconstitute 50- or 100-mg vial by adding 50 or 100 mL of sterile water for injection (do not use bacteriostatic water for injection) respectively, for a concentration of 1 mg/mL. Can be further diluted with NS or D_5W to a concentration of 0.5 mg/mL if necessary. Use reconstituted solution within 8 hours of mixing when stored refrigerated or at room temperature.

Cathflo® Activase® is supplied as lyophilized powder in 2-mg vials. Reconstitute by adding 2.2 mL sterile water for injection to a final concentration of 1 mg/mL. Do not use bacteriostatic water for injection. Mix by gently swirling until the contents are completely dissolved. DO NOT SHAKE. Use reconstituted solution within 8 hours of mixing. Reconstituted solution may be stored refrigerated or at room temperature.

DOSING/ADMINISTRATION

Dose

Postnatal Age - Weight Dosing

These regimens were developed based on population pharmacokinetics, simulations, and subsequent prospective validations. Target concentrations: peak (1 hour after completion of 20 minute infusion)– greater than 24 mg/L, trough (just before dose) less than 3 mg/L[1] [2][3].

Weight	Postnatal Age	
	Younger than 14 days	14 days or older
800 g or less	16 mg/kg/dose every 48 hours	20 mg/kg/dose every 42 hours
801 to 1200 g	16 mg/kg/dose every 42 hours	20 mg/kg/dose every 36 hours
1201 to 2000 g	15 mg/kg/dose every 36 hours	18 mg/kg/dose every 30 hours
2001 to 2800 g	15 mg/kg/dose every 36 hours	18 mg/kg/dose every 24 hours
2800 g or greater	15 mg/kg/dose every 30 hours	18 mg/kg/dose every 20 hours
Smits et al, 2017; Rivera-Chaparro et al, 2017; Smits et al, 2015		

Postnatal Age - Postmenstrual Age Dosing

These regimens were developed by a retrospective pharmacokinetic study (n=278). Target peak concentrations were attained in 84% of neonates (median (interquartile range): gestational age 36.9 weeks (30.1 to 38.9), postnatal age 1 day (0 to 2), and postmenstrual age 37 weeks (33 to 39)). Mean peak and trough concentrations were 28.5+/-5.8 mg/mL and 2+/-1.7 mg/L, respectively. Target concentrations: Peak of (30 minutes after completion of the infusion) 20 to 35 mg/L and trough (30 to 60 minutes before dose) less than 8 mg/L [4].

Postmenstrual Age	Postnatal Age	Dosage
29 weeks or less	0 to 7 days	14 mg/kg/dose every 48 hours
	8 to 28 days	12 mg/kg/dose every 36 hours
	29 days or older	12 mg/kg/dose every 24 hours

30 to 34 weeks	0 to 7 days	12 mg/kg/dose every 36 hours
	8 days or older	12 mg/kg/dose every 24 hours
35 weeks or more	All	12 mg/kg/dose every 24 hours
Hughes, 2017		

Dosage Adjustment
Coadministration with ibuprofen: Prolong the dosing interval by 10 hours when ibuprofen is administered [3].
Hypothermia/Asphyxia: Dose interval was prolonged by 10 hours in neonates with asphyxia in a pharmacokinetic study [3]. Alternatively, dose adjustment was suggested based on a population pharmacokinetic modeling and simulation of retrospectively collected data for near term neonates with perinatal asphyxia treated with therapeutic hypothermia (n=56) [5] combined with published data of preterm and term neonates (n=874) [3][6]. Proposed regimen: 15 mg/kg/dose every 48 h for children between 1,200 g and 2,800 g and 15-mg/kg/ dose every 42 h for neonate above 2,800 g for the first 2 consecutive doses during hypothermia (33.5 degrees C) for target concentrations greater than 24 mg/L for peak and less than 5 mg/L for trough. Less than 17% of dose simulations had trough concentrations more than 5 mg/L [5]
Renal Impairment: Either prolong intervals or reduce dose [7].

Uses

Amikacin was effective for infections caused by gram-negative bacilli that are resistant to other aminoglycosides. Usually used in combination with a β-lactam antibiotic for neonatal sepsis and other severe infections because of the possibility of infections due to gram-positive organisms such as streptococci or pneumococci [7].

Infective endocarditis: The following recommendations are based on a consensus of experts [13]. The full pediatric guidelines can be found here: https://doi.org/10.1161/CIR.0000000000000298

Organism Directed Therapy		
Organism	First-Choice	Alternative Choice
Streptococci		
Highly susceptible to penicillin G (MBC 0.1 mcg/mL or less); includes most viridans streptococci, groups A, B, C, G nonenterococcal, group D	Penicillin G or CefTRIAXone	Vancomycin or First-generation cephalosporin or CefTRIAXone

streptococci (S bovis, S equinus)		
Relatively resistant to penicillin (MBC 0.2 mcg/mL or more); less-susceptible viridans streptococci or enterococci	Penicillin G or Ampicillin + Gentamicin (for first 2 weeks, or entire course for enterococci)	Vancomycin + Gentamicin for enterococci Ampicillin + CefTRIAXone (for aminoglycoside (AMG)-resistant enterococci or AMG-intolerant patient) CefTRIAXone + gentamicin (not for enterococcal endocarditis)
Resistant to penicillin	Consult an infectious disease specialist.	---
Staphylococci (S aureus or coagulase-negative staphylococci) †		
Penicillin G susceptible (1 mcg/mL or less) (rare)	Penicillin G	Oxacillin or Nafcillin or First-generation cephalosporin or Vancomycin
Penicillin G resistant (0.1 mcg/mL)	Oxacillin or Nafcillin with or without Gentamicin	Vancomycin (for those highly allergic to beta-lactam antibiotics) or First-generation cephalosporin
Oxacillin (MRSA) resistant (4 mcg/mL)	Vancomycin	Daptomycin for right-sided endocarditis, maybe for left-sided
Vancomycin resistant or intolerant	Daptomycin	Unknown
	†When prosthetic material present add riFAMpin + gentamicin (for first 2 weeks) for all staphylococci	

Gram-negative enteric bacilli	CefTAZidime or Cefepime or Cefotaxime or CefTRIAXone Plus gentamicin (or tobramycin or amikacin, depending on susceptibility)	Broad-spectrum penicillin Plus gentamicin (or tobramycin or amikacin)
HACEK group	CefTRIAXone or Cefotaxime or Ampicillin-sulbactam	Ampicillin (when susceptible) Plus aminoglycoside
KEY: AMG = aminoglycosides; HACEK = Haemophilus species, Aggregatibacter species, Cardiobacterium hominis, Eikenella corrodens, and Kingella species; MBC = minimum bactericidal concentration, MRSA = methicillin-resistant Staphylococcus aureus (includes resistance to oxacillin, nafcillin, and cephalosporins)		
Baltimore, 2015		

Sepsis

Optimal treatment for suspected, early-onset sepsis is broad-spectrum antimicrobial coverage using a combination of ampicillin and an aminoglycoside (usually gentamicin); once a pathogen is identified, therapy should be narrowed unless synergism is required. Therapy should be discontinued at 48 hours if the probability of sepsis is low. Duration of treatment is usually 10 days for bacteremia without an identifiable focus [14].

There was no difference in failure rate between a 7-day vs 10-day duration of empiric treatment with IV cefTRIAXone and amikacin for culture-proven sepsis in 132 neonates, 1.5 kg or more and gestational age 32 weeks or more, who remitted clinically by day 5 in a randomized study. The follow-up period was 28 days. The median age at presentation was 3 days (2 to 4 days) and 56.8% had early-onset sepsis. The majority of organisms in blood cultures were *Klebsiella* spp. (40.9%), *Staphylococcus aureus* (22.7%), *Enterobacter* spp. (16.7%), and MRSA (7.6%) [15].

Pediatric FDA-Approved Indications

Short-term treatment of serious infections caused by susceptible strains of Gram-negative bacteria, including *Pseudomonas* species, *E. coli*, species of indole-positive and indole-negative *Proteus*, *Providencia* species, *Klebsiella-Enterobacter-Serratia* species, and *Acinetobacter* (*Mima-Herellea*) species [7].

Administration

Dilute to a final concentration of 2.5 to 10 mg/mL [8][9][10][11] and administer as IV infusion by syringe pump over 60 to 120 minutes [12]; in neonatal studies amikacin was infused over 20 minutes [3] and in neonatal pharmacokinetic modeling studies infusion rates of 20 to 30 minutes were applied [6].
Administer as a separate infusion from penicillin-containing compounds. IM injection is associated with variable absorption, especially in the very small infant.

MEDICATION SAFETY

Contraindications/Precautions

Precautions
Administration: *In vitro* mixing of aminoglycosides with beta-lactam antibiotics (penicillin or cephalosporins) may result in a significant mutual inactivation. A reduction in serum half-life or serum level may occur when an aminoglycoside or penicillin-type drug is administered by separate routes. Inactivation of the aminoglycoside is clinically significant only in patients with severely impaired renal function. Inactivation may continue in specimens of body fluids collected for assay, resulting in inaccurate aminoglycoside readings. Such specimens should be properly handled (assayed promptly, frozen or treated with betalactamase) [7]
Gastrointestinal: Clostridium difficile associated diarrhea has been reported and ranged from mild diarrhea to fatal colitis; discontinue use if suspected [7].
Immunologic: Allergic-type reactions, including anaphylaxis and life-threatening or less severe asthmatic reactions, may occur in patients with sulfite sensitivity as preparation contains sodium metabisulfite [7].
Neurologic: Use caution in patients with myasthenia gravis or parkinsonism; muscle weakness may be aggravated [7].
Topical irrigation: Irreversible deafness, renal failure, and death due to neuromuscular blockade have been reported following irrigation of both small and large surgical fields with aminoglycoside preparations [7].

Adverse Effects

Transient and reversible renal tubular dysfunction may occur, resulting in increased urinary losses of sodium, calcium, and magnesium. Vestibular and auditory ototoxicity may occur. The addition of other nephrotoxic and/or ototoxic medications (eg, furosemide, vancomycin) may increase these adverse effects. Increased neuromuscular blockade (ie, neuromuscular weakness and respiratory failure) may occur when used with pancuronium or other neuromuscular blocking agents and in patients with hypermagnesemia.

Black Box Warning

•Patients treated with parenteral aminoglycosides should be under close clinical observation because of the potential ototoxicity and nephrotoxicity associated with their use. Safety for treatment periods which are longer than 14 days has not been established.
•Neurotoxicity, manifested as vestibular and permanent bilateral auditory ototoxicity, can occur in patients with preexisting renal damage and in patients with normal renal function treated at higher doses and/or for periods longer than those recommended. The risk of aminoglycoside-induced ototoxicity is greater in patients with renal damage. High frequency deafness usually occurs first and can be detected only by audiometric testing. Vertigo may occur and may be evidence of vestibular injury. Other manifestations of neurotoxicity may include numbness, skin tingling, muscle twitching and convulsions . The risk of hearing loss due to aminoglycosides increases with the degree of exposure to either high peak or high trough serum concentrations . Patients developing cochlear damage may not have symptoms during therapy to warn them of developing eighth-nerve toxicity, and total or partial irreversible bilateral deafness may occur after the drug has been discontinued. Aminoglycoside-induced ototoxicity is usually irreversible.
•Aminoglycosides are potentially nephrotoxic. The risk of nephrotoxicity is greater in patients with impaired renal function and in those who receive high doses or prolonged therapy.
•Neuromuscular blockade and respiratory paralysis have been reported following parenteral injection, topical instillation (as in orthopedic and abdominal irrigation or in local treatment of empyema), and following oral use of aminoglycosides. The possibility of these phenomena should be considered if aminoglycosides are administered by any route, especially in patients receiving anesthetics; neuromuscular blocking agents such as tubocurarine, succinylcholine, decamethonium; or in patients receiving massive transfusions of citrate-anticoagulated blood. If blockage occurs, calcium salts may reverse these phenomena, but mechanical respiratory assistance may be necessary.
•Renal and eighth-nerve function should be closely monitored especially in patients with known or suspected renal impairment at the onset of therapy and also in those whose renal function is initially normal but who develop signs of renal dysfunction during therapy. Serum concentrations of amikacin should be monitored when feasible to assure adequate levels and to avoid potentially toxic levels and prolonged peak concentrations above 35 micrograms per mL. Urine should be examined for decreased specific gravity, increased excretion of proteins and the presence of cells or casts . Blood urea nitrogen, serum creatinine or creatinine clearance should be measured periodically. Serial audiograms should be obtained where feasible in patients old enough to be tested, particularly high risk patients . Evidence of ototoxicity (dizziness, vertigo, tinnitus , roaring in the ears and hearing loss) or nephrotoxicity requires discontinuation of the drug or dosage adjustment.
•Concurrent and/or sequential systemic, oral or topical use of other neurotoxic or nephrotoxic products, particularly bacitracin, cisplatin, amphotericin B, cephaloridine, paromomycin, viomycin, polymyxin B, colistin, vancomycin, or other aminoglycosides should be avoided. Other factors that may increase risk of toxicity are advanced age and dehydration.
•The concurrent use of amikacin with potent diuretics (ethacrynic acid or furosemide) should be avoided since diuretics by themselves may cause ototoxicity. In addition, when administered intravenously, diuretics may enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue [7].

Solution Compatibility

D_5W, $D_{10}W$, $D_{20}W$, and NS.

Terminal Injection Site Compatibility

Acyclovir, aminophylline, amiodarone, aztreonam, caffeine citrate, calcium chloride, calcium gluconate, cefazolin, cefepime, cefotaxime, cefoxitin, ceftazidime, ceftriaxone, chloramphenicol, cimetidine, clindamycin, dexamethasone, enalaprilat, epinephrine, esmolol, fluconazole, furosemide, heparin (concentrations of 1 unit/mL or less), hydrocortisone succinate, hyaluronidase, linezolid, lorazepam, magnesium sulfate, metronidazole, midazolam, milrinone, morphine, nicardipine, penicillin g, pentobarbital, phenobarbital, potassium chloride, ranitidine, remifentanil, sodium bicarbonate, vancomycin, vitamin K_1, and zidovudine.

Terminal Injection Site Incompatibility

Fat emulsion. Amphotericin B, ampicillin, azithromycin, heparin (concentrations greater than 1 unit/mL), imipenem/cilastatin, mezlocillin, nafcillin, oxacillin, phenytoin, propofol, thiopental, and ticarcillin/clavulanate.

Monitoring

Measure serum concentrations when treating for more than 48 hours. Obtain peak concentration 30 minutes after end of infusion, and trough concentration just prior to the next dose. When treating patients with serious infections or significantly changing fluid or renal status consider measuring the serum concentration 24 hours after a dose, and use the chart below for the suggested dosing interval. Blood samples obtained to monitor serum drug concentrations should be spun and refrigerated or frozen as soon as possible.

Therapeutic serum concentrations

Peak: 20 to 30 mcg/mL (or C_{max} /MIC ratio greater than 8:1)
(Draw 30 minutes after end of infusion, 1 hour after IM injection.)
Trough: 2 to 5 mcg/mL

Suggested Dosing Intervals		
Level at 24 hrs (mcg/mL)	**Half-life (hours)**	**Suggested Dosing Interval (hours)**
≤5	~ 9	24
5.1 to 8.0	~ 12	36
8.1 to 10.5	~ 16	48

≥10.6		Measure level in 24 hours

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action: Amikacin, a semi-synthetic aminoglycoside [7] bactericidal antibiotic, inhibits normal protein synthesis in susceptible microorganisms [16]. Amikacin resists degradation by most aminoglycosides inactivating enzymes known to affect gentamicin, tobramycin, and kanamycin [7].

Pharmacokinetics
[4]

Postmenstrual Age	Postnatal Age	Half-life	Volume of distribution
29 weeks or less	0 to 7 days (n=41)	11 hours	0.414 L/kg
	8 to 28 days (n=9)	9.64 hours	0.472 L/kg
	29 days or older (n=2)	4.93 hours	0.353 L/kg
30 to 34 weeks	0 to 7 days (n=49)	7.96 hours	0.462 L/kg
	8 days or older (n=16)	6.20 hours	0.454 L/kg
35 weeks or more	All ages (n=170)	6.21 hours	0.433 L/kg
Comorbidity			
Congenital heart disease (n=38)*		6.97 hours	0.449 L/kg
*Congenital heart disease = cyanotic heart defect or acyanotic heart defect requiring surgical intervention prior to or during amikacin therapy			
Hughes et al, 2017			

Volume of distribution: 0.833 L in 874 neonates (postnatal age 1 to 30; gestational age 24 to 43 weeks) [6]
Clearance: 0.493 L/hr in 874 neonates (postnatal age range, 1 to 30; gestational age range, 24 to 43 weeks). Coadministration of ibuprofen reduced clearance [6].
0.84 L/hr/70 kg at 28 weeks postmenstrual age (PMA), 1.23 L/hr/70 kg at 34 weeks PMA, and 1.56 L/hr/70 kg at 40 weeks PMA in a pharmacokinetic study of 715 neonates (PMA 24 to 43 weeks; weight 0.385 to 4.78 kg). Clearance was affected the most by size (66%), PMA (17%), and renal function (9%) [17].

Therapeutic Hypothermia for Asphyxia: Clearance was reduced by 40.6% in neonates with perinatal asphyxia treated with therapeutic hypothermia (PATH) compared with neonates without PATH in model-based approach pharmacokinetic study. Volume of distribution did not change [5].

ABOUT

Special Considerations/Preparation

Availability: 250 mg/mL in 2-mL and 4-mL vials [7]
For IV use, dilute with a compatible solution to a concentration of 2.5 to 10 mg/mL [7][8].
Stability: Solutions, 0.25 and 5 mg/mL, are stable for 24 hours at room temperature. Solutions stored for 60 days at 4 degrees C and then stored at 25 degrees C had utility times of 24 hours. At concentrations of 0.25 and 5 mg/mL, solutions frozen (-15 degrees C) for 30 days, thawed, and stored at 25 degrees C had utility times of 24 hours [7]

Aminocaproic Acid

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Hemorrhage Prophylaxis
Extracorporeal membrane oxygenation (ECMO): 100 mg/kg followed by 30 mg/kg/hr. Administer directly to the patient via IV or through the ECMO circuit. Duration of infusion 72 hours or longer if bleeding persists or shorter if cannula is removed [1][2]

Uses

Hemorrhage Prophylaxis
Cardiopulmonary bypass (CPB): In a neonatal subgroup analysis (n=4426) of a large observational study (n=22,258), aminocaproic acid had greater bleeding requiring surgical intervention compared with aprotinin [4]. There was higher blood loss with aminocaproic acid (46 mL/kg) compared with aprotinin (36 mL/kg), but no differences in need for transfusion or requirement for surgical revision in 235 neonates who underwent CPB in a nonrandomized study [5]. There was no difference in blood loss, requirement for surgical revision due to bleeding, or need for transfusion between tranexamic acid and aminocaproic acid in 105 neonates who underwent CPB in a nonrandomized study [6]. Various dosing regimens are available. A pharmacokinetic study in 10 neonates proposed 40 mg/kg IV loading dose followed by 30 mg/kg/hr infusion and a priming dose of 100 mg/L [7]. In clinical studies, 75 mg/kg IV over 10 minutes was administered at the beginning and end of CPB. Additionally, 75 mg/100 mL was added to the priming volume of the CPB system [5][6]. A pharmacokinetic study identified the following regimen to achieve therapeutic concentrations: 75 mg/kg IV loading dose over 10 minutes followed by 75 mg/kg/hr IV until the end of surgery. Additionally, add 75 mg/kg in the priming volume of the CPB system (venous reservoir) [8].

Hemorrhage Prophylaxis
Extracorporeal membrane oxygenation (ECMO): Empiric bleeding protocols included aminocaproic acid 100 mg/kg followed by 30 mg/kg/hr. Duration of infusion was for 72 hours or longer if bleeding persisted or shorter when cannula was removed. Administration was either directly to the patient or through the ECMO circuit [1][2]. Surgical site bleeding was reduced with aminocaproic acid (7%) compared with no aminocaproic acid (12%) [2]. However, aminocaproic acid did not reduce the incidence of neonatal intracranial hemorrhage compared with no aminocaproic acid in 2 studies (n=327) [2][9]. Reduced circuit times due to clotting may not be a concern, as a retrospective analysis of 164 patients on ECMO demonstrated that a bleeding protocol, which included aminocaproic acid, did not shorten circuit times [1].

Administration

IV: Rapid administration of undiluted injection into a vein is not recommended .
The manufacturer recommends a concentration of 16 to 20 mg/mL [3].

MEDICATION SAFETY

Contraindications/Precautions

Contraindicated in DIC without concomitant heparin [10][3].

Intrarenal obstruction and glomerular capillary thrombosis has been reported in patients with upper urinary tract bleeding. Avoid use in patients with hematuria of upper urinary tract origin or use with caution if benefit of therapy outweighs the risk. Rare cases of skeletal muscle weakness, necrosis of muscle fibers, and rhabdomyolysis have been reported with prolonged administration. Neurological deficits, including hydrocephalus, cerebral ischemia, and cerebral vasospasm, have been reported with the use of antifibrinolytic agents in patients with subarachnoid hemorrhage (causality is unknown). Only use when hyperfibrinolysis (hyperplasminemia) has been definitively diagnosed. Rapid injection may result in hypotension, bradycardia, and/or arrhythmia. Thrombophlebitis may occur. Avoid concomitant use with factor IX complex concentrates or anti-inhibitor coagulant concentrate [10][3].

Injection contains benzyl alcohol, which has been associated with serious adverse effects, including death, in neonates and low-birth-weight infants [3].

Adverse Effects

Renal risk (28.6% vs 36.8%), renal injury (3.6% vs 9.5%), renal failure (1.4% vs 1.2%), vascular thrombosis (12.1% vs 8.4%), seizures (2.9% vs 3.2%), intracranial bleeding (3.6% vs 4.2%), stroke (1.4% vs 0%), and in-hospital mortality (6.4% vs 8.4%) occurred in 235 neonates undergoing cardiopulmonary bypass and administration of aminocaproic acid and aprotinin, respectively [5]. A fatal case of aortic thrombosis in a neonate on extracorporeal life support and receiving aminocaproic acid occurred [11].

Solution Compatibility

D_5W, NS, Ringer injection.

Terminal Injection Site Compatibility

Aminocaproic acid 20 mg/mL
Amikacin (5 mg/mL), aminophylline (2.5 mg/mL), amphotericin B conventional colloidal (0.6 mg/mL), amphotericin B liposome 1 mg/mL), ampicillin (20 mg/mL), ampicillin/sulbactam (20/10 mg/mL), atracurium (0.5 mg/mL), azithromycin (2 mg/mL), aztreonam (40 mg/mL), bumetanide (40 mcg/mL), calcium chloride (40 mg/mL), calcium gluconate (40 mg/mL), cefazolin (20 mg/mL), cefepime (20 mg/mL), cefotaxime (20 mg/mL), cefotetan (20 mg/mL), cefoxitin 20 (mg/mL), ceftazidime (40 mg/mL), ceftazidime (l-arginine) (40 mg/mL), ceftriaxone (20 mg/mL), cefuroxime (30 mg/mL), cimetidine (12 mg/mL), cisatracurium (0.5 mg/mL), clindamycin (10 mg/mL), cyclosporine (5 mg/mL), dexamethasone (1 mg/mL), digoxin (0.25 mg/mL), diltiazem (5 mg/mL), diphenhydramine (2 mg/mL), dobutamine (4 mg/mL), dopamine (3.2 mg/mL), enalaprilat (0.1 mg/mL), epinephrine (50 mcg/mL), erythromycin (5 mg/mL), esmolol (10 mg/mL), famotidine (2 mg/mL), fentanyl (50 mcg/mL), fluconazole (2 mg/mL), foscarnet (24 mg/mL), fosphenytoin (20 mgPE/mL), furosemide (3 mg/mL), gentamicin (5 mg/mL), granisetron (50 mcg/mL), haloperidol (0.2 mg/mL), heparin (100 units/mL), hydrocortisone (1 mg/mL), hydromorphone (0.5 mg/mL), imipenem/cilastatin (5 mg/mL), isoproterenol (20 mcg/mL), ketorolac (15 mg/mL), labetalol (2 mg/mL), levofloxacin (5 mg/mL), lidocaine (10 mg/mL), linezolid (2 mg/mL), lorazepam (0.5 mg/mL), magnesium (100 mg/mL), mannitol (150 mg/mL) (15%), meropenem (2.5 mg/mL), methylprednisolone (5 mg/mL), metoclopramide (5 mg/mL), metronidazole (5 mg/mL), milrinone (0.2 mg/mL), morphine (15 mg/mL), nalbuphine (10 mg/mL), naloxone (0.4 mg/mL), nitroglycerin (0.4 mg/mL), nitroprusside (2 mg/mL), ondansetron (1 mg/mL), pancuronium (0.1 mg/mL), pentobarbital (5 mg/mL), phenobarbital (5 mg/mL), phenylephrine (1 mg/mL), piperacillin (40 mg/mL), piperacillin/tazobactam (40/5 mg/mL), potassium chloride (0.2 mEq/mL), procainamide (20 mg/mL), propranolol (1 mg/mL), ranitidine (2 mg/mL), rocuronium (1 mg/mL), sargramostim (10 mcg/mL), sodium bicarbonate (1 mEq/mL), succinylcholine (2 mg/mL), sulfamethoxazole/trimethoprim (4/0.8 mg/mL), tacrolimus (20 mcg/mL), ticarcillin/clavulanate (31 mg/mL), tobramycin (5 mg/mL), vancomycin (10 mg/mL), vecuronium (1 mg/mL), verapamil (2.5 mg/mL), zidovudine (4 mg/mL).

Aminocaproic acid 50 mg/mL
Amphotericin B lipid complex (1 mg/mL), argatroban (1 mg/mL), bivalirudin (5 mg/mL), daptomycin (10 mg/mL), dexmedetomidine (4 mcg/mL), ertapenem (20 mg/mL), moxifloxacin (1.6 mg/mL), octreotide (5 mcg/mL), palonosetron (50 mcg/mL), pantoprazole (0.4 mg/mL), vasopressin (1 unit/mL), voriconazole (4 mg/mL).

Terminal Injection Site Incompatibility

Acyclovir, amiodarone, caspofungin, ciprofloxacin, diazepam, dolasetron, doxycycline hyclate, filgrastim, ganciclovir, midazolam, mycophenolate mofetil, nicardipine, phenytoin, quinupristin/dalfopristin.

Compatibility information refers to physical compatibility and is derived from Trissel's™ 2 Clinical Pharmaceutics Database. The determination of compatibility is based on concentrations for administration recommended herein. Drug compatibility is dependent on

multiple factors (eg, drug concentrations, diluents, storage conditions). This list should not be viewed as all-inclusive and should not replace sound clinical judgment. The user is referred to Trissel's™ 2 for more complete details.
Trissel's™ 2 Clinical Pharmaceutics Database, version updated on 09/15/2013.

Monitoring

Monitor CPK levels in patients on long-term therapy. Assess the amount of fibrinolysis present during therapy [10][3].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Aminocaproic acid inhibits fibrinolysis through plasminogen activator inhibition (principal) and antiplasmin activity (lesser extent). Apparent Vd (mean +/- SD), 23.1 +/- 6.6 L (oral) and 30 +/- 8.2 L (IV). Distributes throughout extravascular and intravascular compartments, penetrating RBCs and other tissues with prolonged administration. Primarily excreted renally as unchanged drug (65%) and the metabolite adipic acid (11%). Renal clearance, 116 mL/min. Total body clearance, 169 mL/min. Terminal elimination half-life, approximately 2 hours [10][3].

A suggested regimen of aminocaproic acid 40 mg/kg IV loading dose followed by a 30 mg/kg/hr infusion and a priming dose of 100 mg/L would achieve a target concentration above 50 mg/L in most neonates during cardiopulmonary bypass surgery. The aminocaproic acid regimen was developed using aminocaproic pharmacokinetic values from 10 neonates who underwent elective cardiac surgery with cardiopulmonary bypass [7].
The minimum effective concentration of aminocaproic acid required to inhibit fibrinolysis in plasma from 20 term neonates 44.2 mcg/mL, which was significantly less than that for adults (131.4 mcg/mL) [12].
Aminocaproic acid concentration range was 39 to 433 mcg/mL (mostly within 110 to 350 mcg/mL) in 42 neonates on extracorporeal membrane oxygenation and receiving aminocaproic acid 100 mg/kg IV bolus followed by 30 mg/kg/hr IV. Concentration exceeded 1000 mcg/mL in one neonate with renal and hepatic insufficiency; no complications occurred [13].

ABOUT

Special Considerations/Preparation

IV solution: Available as an IV solution containing 250 mg/mL aminocaproic acid with 0.9%

benzyl alcohol. [3].
Dilute with NS, D5W, or LR. Sterile water for injection may also be used, but will produce a hypo-osmolar solution [3].

Aminophylline

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Loading dose: 8 mg/kg IV infusion over 30 to 60 minutes, or orally.
Maintenance dose: 1.5 to 3 mg/kg/dose orally, or IV every 8 to 12 hours (start maintenance dose 8 to 12 hours after the loading dose).

In preterm infants, changing from IV aminophylline to oral theophylline requires no dose adjustment.

Uses

Apnea: Pharmacological treatment with caffeine is the standard of care for apnea of prematurity [7].

Treatment of neonatal apnea, including post-extubation, post-anesthesia, and prostaglandin E_1-induced. Bronchodilator. May improve respiratory function.

Administration

Intravenous bolus over 30 to 60 minutes [1][2][3][4][5]. May give as 25-mg/mL concentration or further dilute to as low as 1 mg/mL for continuous infusion [6].

MEDICATION SAFETY

Adverse Effects

GI irritation. Hyperglycemia. CNS irritability and sleeplessness. May be associated with renal calcifications when used concurrently with furosemide and/or dexamethasone.
Signs of toxicity: Sinus tachycardia, failure to gain weight, vomiting, jitteriness, hyperreflexia, and seizures.

Treatment of Serious Theophylline Toxicity: Activated charcoal, 1 g/kg as a slurry by gavage tube every 2 to 4 hours. Avoid sorbitol-containing preparations: They may cause osmotic diarrhea.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Acyclovir, ampicillin, amikacin, aztreonam, caffeine citrate, calcium gluconate, ceftazidime, chloramphenicol, cimetidine, dexamethasone, dopamine, enalaprilat, erythromycin lactobionate, esmolol, famotidine, fluconazole, flumazenil, furosemide, heparin, hydrocortisone succinate, lidocaine, linezolid, meropenem, metoclopramide, midazolam, morphine, nafcillin, nicardipine, nitroglycerin, pancuronium bromide, pentobarbital, phenobarbital, piperacillin, piperacillin/tazobactam, potassium chloride, propofol, prostaglandin E_1, ranitidine, remifentanil, sodium bicarbonate, vancomycin, and vecuronium.

Terminal Injection Site Incompatibility

Amiodarone, cefepime, ceftriaxone, ciprofloxacin, clindamycin, dobutamine, epinephrine, hydralazine, insulin, isoproterenol, methylprednisolone, and penicillin G.

Monitoring

Monitor heart rate and check blood glucose periodically with reagent strips. Assess for agitation and feeding intolerance.

Consider withholding next dose if heart rate is greater than 180 beats per minute.

When indicated by lack of efficacy or clinical signs of toxicity, serum trough concentration should be obtained. Therapeutic ranges are:
1) Apnea of prematurity: 7 to 12 mcg/mL.
2) Bronchospasm: 10 to 20 mcg/mL (older infants with bronchospasm may need these higher levels because of increased protein binding).

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Stimulates central respiratory drive and peripheral chemoreceptor activity. May increase diaphragmatic contractility. Cerebral blood flow is acutely decreased following IV bolus dose. Renal effects include diuresis and increased urinary calcium excretion. Stimulates gastric acid secretion and may cause gastroesophageal reflux. Cardiac output is increased due to higher sensitivity to catecholamines. Elimination in preterm infants is primarily as unchanged drug, although significant interconversion to caffeine occurs. In the very immature neonate, the serum half-life of theophylline is prolonged (20 to 30 hours). Theophylline metabolism and clearance mature to adult values by 55 weeks postmenstrual age. Aminophylline salt is 78.9% theophylline. Theophylline administered orally is approximately 80% bioavailable; therefore, no dosage adjustment is necessary when changing from IV aminophylline to oral theophylline.

ABOUT

Special Considerations/Preparation

Availability: Aminophylline for IV use (25 mg/mL) in 10- and 20-mL vials. Dilute 1 mL (25 mg) with 4 mL NS or D_5W to yield a final concentration of 5 mg/mL. Stable for 4 days refrigerated.

Oral theophylline is available only as an elixir at a concentration of 80 mg/15 mL (5.33 mg/mL) and contains 20% alcohol.
Aminophylline oral solution is no longer available.

Extemporaneous Suspension
Oral aminophylline 3 mg/mL liquid suspension made with aminophylline injection 25 mg/mL and mixed with 1:1 Ora Sweet/Ora Plus was stable for 91 days at 4°C and 25° C. Store in amber glass bottle [8]

Amiodarone

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

IV Loading Dose: 5 mg/kg IV infusion given over 20 to 60 minutes, preferably in a central vein.

Maintenance Infusion: 7 to 15 mcg/kg/minute (10 to 20 mg/kg per 24 hours). Begin at 7 mcg/kg/minute and titrate by monitoring effects. For infusions lasting longer than 1 hour, amiodarone IV concentrations should not exceed 2 mg/mL unless using a central line.

Consider switching to oral therapy within 24 to 48 hours.

Correct hypokalemia, hypomagnesemia, and hypocalcemia prior to initiating treatment[1].
Oral: 5 to 10 mg/kg/dose every 12 hours.

Uses

Arrhythmias: Treatment of life-threatening or drug-resistant refractory supraventricular (SVT), ventricular tachyarrhythmias (VT), and postoperative junctional ectopic tachycardia (JET) - see Adverse Effects.

Administration

Dilute the IV loading dose to 1.5 mg/mL [2] and infuse over 20 to 60 minutes [3]. For IV infusion, dilute to a concentration of 1 to 6 mg/mL in compatible diluent. **For infusions lasting longer than 1 hour (eg, continuous infusion), amiodarone IV concentrations should not exceed 2 mg/mL unless using a central line. When infusing the original amiodarone product, infusions lasting longer than 2 hours should be administered in glass or polyolefin bottles containing D5W; use of evacuated glass containers is not recommended as precipitation may occur from the buffer** [4]. An in-line filter should be used during administration. Administration via a central catheter is preferred [5].

Extravasation Management Neonatal data are limited to pooled data from 10 case reports/case series (n=237) and are not specific to amiodarone extravasation; subcutaneous saline irrigation with or without hyaluronidase infiltration was commonly used. No standardized management was established. An option for more severe injuries (stages 3 and 4) is subcutaneous irrigation with saline, but this is not advocated as standard treatment.

Conservative management is appropriate for mild extravasation (stages 1 and 2) [6].
Although not neonatal-specific, the following are recommendations for extravasation of acidic or alkaline agents (amiodarone is acidic with a pH ranging from 3.5 to 4.5) [7]

- **General:**
- Stop and disconnect infusion; do not remove the cannula or needle
- Attempt to gently aspirate as much extravasated agent as possible; avoid manual pressure
- Remove cannula or needle
- Dry heat and elevation
- Closely monitor for signs of coagulation and ischemia
- Avoid attempt at pH neutralization (amiodarone - pH 3.5 to 4.5)
- Monitor and consider the need for surgical management such as surgical flushing with normal saline or debridement and excision of necrotic tissue (especially if pain persists for 1 to 2 weeks). In cases of compartment syndrome, surgical decompression may be required
- **Refractory Events:**
- Hyaluronidase 15 units intradermally along injection site and edematous area. Give as five, 0.2-mL intradermal injections along extravasation site and edematous tissue.
- **Inadvertent Intraarterial Administration:**
- Leave inadvertent intraarterial line in place for diagnostics
- Systemic heparin titrated to therapeutic anticoagulant effect.
- Stellate ganglion block

MEDICATION SAFETY

Contraindications/Precautions

Contraindications
Cardiogenic shock [9][19]
Hypersensitivity to amiodarone or to any of its components, including iodine [9][19]
Sick sinus syndrome, second- or third-degree atrioventricular block, bradycardia leading to syncope without a functioning pacemaker [1].
Severe sinus bradycardia or second or third degree atrioventricular block, if no pacemaker is present [9]

Precautions
Administration: The IV formulation should only be administered when access to facilities equipped to monitor for effectiveness and side effects are available, and by physicians experienced in the treatment of life-threatening arrhythmias [20].
Adverse events: Due to the long half-life, adverse events can persist for several weeks following discontinuation [1]

Cardiovascular: Hypotension, including some refractory and fatal cases, has been reported, particularly with IV administration; monitoring recommended [9].
Cardiovascular: Exacerbation of presenting arrhythmia, new ventricular fibrillation, incessant ventricular tachycardia, increased resistance to cardioversion, and polymorphic ventricular tachycardia with QTc prolongation (Torsade de Pointes) may occur [1]
Cardiovascular: Bradycardia has been reported,[12] especially with concomitant use of drugs that slow heart rate (eg, digoxin, beta blockers, verapamil, diltiazem, ivabradine, clonidine) or by presence of electrolyte disorders [1]) and with concomitant use of ledipasvir/sofosbuvir or sofosbuvir with simeprevir [1]. Monitoring recommended with concomitant use or recent discontinuation of amiodarone when starting antiviral treatment [1] Discontinuation or dose adjustment may be required [12]..
Cardiovascular: Atrioventricular block has been reported. Discontinuation or dose adjustment may be required [12].
Cardiovascular: Preexisting implanted defibrillator or pacemaker may result in changes to electrical conduction properties (pacing or defibrillating thresholds) of heart; monitoring recommended with oral administration [1].
Cardiovascular: Hypotension, including some refractory and fatal cases, has been reported, particularly with IV administration; monitoring recommended [9][19].
Concomitant use: Avoid drugs that prolong the QT interval [9].
Concomitant use: Avoid grapefruit juice [9].
Dermatologic: Phlebitis has been reported, especially with IV concentrations greater than 3 mg/mL [12].
Dermatologic: Photosensitivity has been reported and may be reduced with sun-barrier creams or protective clothing. Blue-gray skin discoloration may occur with prolonged use; some reversal of discoloration may occur upon discontinuation [1].
Discontinuation: Treatment discontinuation or dosage adjustment of oral therapy may cause unpredictable recurrence of previously controlled life-threatening arrhythmia; patient may require prolonged hospitalization [19].
Endocrine and metabolic: Thyroid abnormalities, including hypothyroidism, hyperthyroidism and myxedema coma (sometimes fatal), thyroid nodules, and thyroid cancer, have been reported; increased risk for potentially fatal thyrotoxicosis and arrhythmia breakthrough or exacerbation; monitoring recommended and dosage adjustment or discontinuation may be necessary [1].
Endocrine and metabolic: Thyroid abnormalities including increased triiodothyronine (T3) and inactive reverse (T3) may occur in euthyroid patients; monitoring recommended particularly in elderly patients and any patient with a history of thyroid nodules, goiter, or other thyroid dysfunction [12]
Endocrine and metabolic: Hyperthyroidism, including arrythmia breakthrough, and hypothyroidism may occur; dose adjustment or discontinuation may be necessary [12]
Endocrine and metabolic: Preexisting hypokalemia or hypomagnesemia may exaggerate degree of QT prolongation and increase potential for torsade de pointes; increased risk in patients with severe or prolonged diarrhea or those receiving diuretics, laxatives, systemic corticosteroids, or amphotericin B. Correct prior to treatment [1] when possible [9].
Endocrine and metabolic: Prior inadequate dietary iodine intake may increase incidence of amiodarone-induced hyperthyroidism [9].
Hepatic: Elevation of liver enzymes has been reported [9]; life-threatening hepatic injury may occur with histology similar to alcoholic hepatitis or cirrhosis. Monitoring recommended and discontinuation or dose reduction may be necessary [1].
Hepatic: Hepatocellular necrosis leading to hepatic coma, acute renal failure, and death have occurred with IV administration at higher than recommended loading dose

concentration and rate of infusion [9].
Immunologic: Potentially fatal anaphylactic or anaphylactoid reactions have been reported with IV administration, including shock (sometimes fatal), cardiac arrest, and the following manifestations: hypotension, tachycardia, hypoxia, cyanosis, rash, flushing, hyperhidrosis, and cold sweat [20].
Neurologic: Chronic administration may lead to peripheral neuropathy, which may not resolve when therapy is discontinued [1]
Ophthalmic: Optic neuritis and optic neuropathy, in some cases resulting in visual impairment that led to blindness, have been reported and may occur at any time during therapy. Discontinuation may be required [1]; monitoring recommended [9].
Ophthalmic: Corneal microdeposits have been reported and may result in visual halos or blurred vision; usually resolve upon dose reduction or discontinuation but asymptomatic microdeposits do not require dose change or discontinuation [1].
Ophthalmic: Corneal refractive laser surgery is contraindicated by most manufacturers of corneal refractive laser surgery devices [9].
Respiratory: Pulmonary toxicity, sometimes fatal, may occur presenting with cough and progressive dyspnea and resulting from either indirect (hypersensitivity pneumonitis, including eosinophilic pneumonia) or direct toxicity (interstitial/alveolar pneumonitis). Monitoring recommended. Consider alternative antiarrhythmic therapy if the patient experiences signs or symptoms of pulmonary toxicity [1].
Respiratory: Pulmonary infiltrates or fibrosis have been reported [19] and is sometimes fatal. Monitoring recommended [12]
Surgery: Increases sensitivity to myocardial depressant and conduction effects of halogenated inhalational anesthetics; perioperative monitoring recommended [1]

Adverse Effects

Common: In adult clinical trials: hypo- or hyperthyroidism, congestive heart failure, cardiac arrhythmias, SA node dysfunction, nausea, vomiting, constipation, anorexia, abdominal pain, solar dermatitis/photosensitivity, malaise/fatigue, tremor/abnormal involuntary movements and other neurologic adverse events, visual disturbances, abnormal liver function tests, pulmonary infiltration or fibrosis, flushing, coagulation abnormalities. Blue skin discoloration, rash, hypotension, and cardiac conduction abnormalities were reported less commonly [1].
Endocrine: In 190 pediatric patients, 33 (17.3%) developed subclinical hypothyroidism within a median time of 7 days (2 to 23 days) of amiodarone initiation and 26 (13.7%) developed hypothyroidism within 11 days (6 to 17 days) in a retrospective chart review. Those with subclinical hypothyroidism became euthyroid (21 out of 33) without thyroid hormone replacement. Those with hypothyroidism experienced normalization (7 out of 26) of thyroid stimulating hormone within a median of 30 days (18 to 67 days). Of the remaining 18 patients with hypothyroidism, 15 started on levothyroxine. Hyperthyroidism occurred in 4 (2.1%) patients with 3 of the 4 treated with methimazole [10].
Short-term toxicity: Bradycardia and hypotension (possibly associated with rapid rates of infusion) may occur. Hypotension may be due, in part, to the co-solvents, polysorbate 80 and benzyl alcohol, which are components of the original amiodarone product [21][22]. In a study of pediatric patients (n=61), ages 30 days to 15 years, hypotension and bradycardia were reported in 36% and 20% of patients, respectively. AV block was reported in 15% of patients [23]. Acute pulmonary toxicity was reported in an infant after IV administration [24].

May potentiate development of ventricular tachycardia and cardiac arrest in the presence of congenital long QT syndrome [25]. Irritating to the peripheral vessels (concentrations greater than 2 mg/mL). Administration through central vein preferred [26].

Long-term toxicity: Thyroid abnormalities (6.3% to 20%) including hyperthyroidism (due to inhibition of T4 to T3) and hypothyroidism (due to high concentration of inorganic iodine) may occur. Photosensitivity reactions (2% to 40%), keratopathy (12% to 30%), rash (3%), and sleep disturbances/behavioral changes (6%) are common adverse events in children. Elevations in liver enzymes have been reported. Hepatitis and cholestatic hepatitis occur rarely (3%). Nausea and vomiting (greater than 10%), optic neuritis (4% to 9%), and pulmonary fibrosis (4% to 9%) have been reported with prolonged oral use in adults. Generic formulation contains 2% benzyl alcohol (20 mg/mL) [27][28][29].

Black Box Warning

Warning: Pulmonary, Hepatic and Cardiac Toxicity
Amiodarone oral tablet is intended for use only in patients with the indicated life-threatening arrhythmias because its use is accompanied by substantial toxicity.
Amiodarone can cause pulmonary toxicity (hypersensitivity pneumonitis or interstitial/alveolar pneumonitis) that has resulted in clinically manifest disease at rates as high as 17% in some series of patients. Pulmonary toxicity has been fatal about 10% of the time. Obtain a baseline chest X-ray and pulmonary-function tests, including diffusion capacity, when therapy is initiated. Repeat history, physical exam, and chest X-ray every 3 to 6 months.
Amiodarone can cause hepatoxicity, which can be fatal. Obtain baseline and periodic liver transaminases and discontinue or reduce dose if the increase exceeds three times normal, or doubles in a patient with an elevated baseline. Discontinue if the patient experiences signs or symptoms of clinical liver injury.
Amiodarone can exacerbate arrhythmias. Initiate in a clinical setting where continuous electrocardiograms and cardiac resuscitation are available [1].

Solution Compatibility

D_5W, and NS at concentrations of 1 to 6 mg/mL.

Terminal Injection Site Compatibility

Amikacin, amphotericin B, atropine, calcium chloride, calcium gluconate, ceftizoxime, ceftriaxone, cefuroxime, clindamycin, dobutamine, dopamine, epinephrine, famotidine, fentanyl, fluconazole, furosemide, esmolol, erythromycin, gentamicin, insulin, isoproterenol, lidocaine, lorazepam, metronidazole, midazolam, milrinone, morphine, nitroglycerin, norepinephrine, penicillin G, phentolamine, potassium chloride, procainamide, tobramycin, vancomycin, and vecuronium.

Terminal Injection Site Incompatibility

Aminophylline, ampicillin, ceftazidime, cefazolin, digoxin, heparin, imipenem-cilastatin, mezlocillin, micafungin, piperacillin, piperacillin-tazobactam, sodium bicarbonate, and sodium nitroprusside.

Monitoring

Therapeutic Monitoring
Physical Exam
• Arrhythmia control is indicative of efficacy [8].
• Stabilization of ventricular arrhythmias is indicative of efficacy [9]

Toxic Monitoring
Laboratory Parameters
• Obtain baseline and periodic liver transaminases [1].
• Monitor thyroid function prior to treatment and periodically thereafter, particularly in patients with a history of thyroid nodules, goiter, or other thyroid dysfunction [1][9]. Investigators recommended weekly monitoring of complete thyroid-function panel for the first 5 weeks after initiation of amiodarone, then less frequently (e.g. every 3 months) or more frequently if signs or symptoms developed for thyroid dysfunction based on a retrospective study of 190 pediatric patients on amiodarone with thyroid-function testing [10].
• Monitor hemodynamic status carefully (eg, lactate levels), especially in young infants and hemodynamically compromised patients [11].
Physical Exam
• Perform baseline chest x-ray and pulmonary-function tests,[12] including diffusion capacity; reevaluate with history, physical exam, and chest x-ray every 3 to 6 months thereafter or if symptoms occur [1], especially in patients receiving chronic treatment [12].
• Perform regular ophthalmic examinations, including funduscopy and slit-lamp examination [1] especially if symptoms of visual impairment appear [12]. Early detection of optic neuritis or neuropathy may be improved with ophthalmologic examinations within the first 12 months, and especially within the first 4 months of therapy [13].
• Assess pacing and defibrillation thresholds at initiation and during therapy in patients with implanted defibrillators or pacemakers [1].
• Monitor for QTc prolongation during IV infusion [9]
• Carefully monitor for evidence of progressive liver injury [9]
• Monitor heart rate in patients receiving concomitant drugs that slow heart rate, such as drugs with depressant effects on the sinus and AV node (eg, digoxin, beta blockers, verapamil, diltiazem, ivabradine, clonidine) [14][15].
• Monitor heart rate in patients taking or recently discontinuing amiodarone when starting antiviral treatment [1][14].
• Monitor for new respiratory symptoms [12]
• Monitor hemodynamic status carefully (eg, blood pressure, heart rate), especially in young infants and hemodynamically compromised patients [11].

• Ophthalmologic exams (funduscopy and slit-lamp examination) should be performed regularly to detect any visual disturbances [16][17][18]

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Class III antiarrhythmic agent that is an iodinated benzofuran compound. Electrophysiologic activity is accomplished by prolonging the duration of the action potential and increasing the effective refractory period. Increases cardiac blood flow and decreases cardiac work and myocardial oxygen consumption. Highly protein bound (95%) in adults. Extensively metabolized to an active metabolite by the cytochrome CYP3A isoenzyme system (limited in preterm infants). Drug-drug interaction potentially occur when given in combination with drugs that inhibit cytochrome CYP3A: phenytoin, fosphenytoin, clarithromycin, erythromycin, azole antifungals (e.g. fluconazole, ketoconazole, itraconazole), protease inhibitors (e.g. indinavir, ritonavir), class IA and class III antiarrhythmics (e.g. quinidine, procainamide, sotalol) and cimetidine (amiodarone levels increase). Amiodarone and its major metabolite may inhibit CYP2C9, CYP2C19, CYP2D6, CYP3A, CYP2A6, CYP2B6, and CYP2C8, as well as the transporters P-glycoprotein and organic cation transporter (OCT2). Amiodarone prevents the elimination of digoxin resulting in high digoxin levels. Half-life reported to be 26 to 107 days in adults. No data in preterm infants. Accumulates in tissues; serum levels can be detected for months. Contains 37.3% iodine by weight. Adheres to PVC tubing: low infusion rates in neonates may lead to reduced drug delivery during continuous infusions. Oral absorption is variable with approximately 50% bioavailability.

ABOUT

Special Considerations/Preparation

IV: The preferred formulation is Nexterone®, available as 1.5 mg/mL (150 mg/100 mL) and 1.8 mg/mL (360 mg/200 mL) concentrations in premix bags. Nexterone® does not contain benzyl alcohol or polysorbate 80, and therefore does not carry a warning regarding benzyl alcohol and fatal gasping syndrome in neonates. There are also no limitations regarding compatibility and stability with plastics and isotonic infusion fluids. Store at room temperature and protect from light.

Generic amiodarone is also available as 50 mg/mL concentration in 5, 10, and 20 mL vials. Contains 2% (20 mg/mL) of benzyl alcohol and 10% (100 mg/mL) polysorbate (Tween) 80 as a preservative. Store at room temperature and protect from light.

Preparation

(Premixed injection) is available as a single-use, ready-to-use, iso-osmotic solution in dextrose for intravenous IV administration. No further dilution is required. Discard any unused portion after use [12].

(Premixed injection) If the administration port protector is damaged, detached, or not

present, discard the container as the solution path sterility may be compromised. Check for minute leaks prior to use by squeezing the bag firmly. If leaks are detected, discard solution as sterility may be impaired. Protect from light until ready to use [12].

Oral:

Supplied in 100-mg, 200-mg, 300-mg, and 400-mg tablets.

Extemporaneous Oral Suspension (5 mg/mL)

Amiodarone 5 mg/mL oral suspension [30]:

- Crush five 200-mg tablets into a mortar and make to a fine powder.
- For the vehicle: Mix 100 mL of Ora-Sweet (or Ora-Sweet Sugar Free) with 100 mL of Ora-Plus, then adjust pH. Use sodium bicarbonate solution (5 gm/100 mL in distilled water) to adjust pH between 6 and 7.
- Add a small amount of vehicle to powder in mortar and make a uniform paste.
- Add additional vehicle in geometric portions while mixing.
- Transfer to graduate and add sufficient amount of vehicle to a total volume of 200 mL

The 5 mg/mL suspension in plastic bottles is stable for at least 42 days at 25 degrees C and 91 days at 4 degrees C

Alternatively, an oral suspension with a final concentration of 5 mg/mL may be made as follows: crush a 200-mg tablet, slowly mix in 20 mL of 1% methylcellulose, and then add in 20 mL of simple syrup to make a total volume of 40 mL. Stable for six weeks at room temperature and three months refrigerated when stored in glass or plastic [31].

Amoxicillin

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Usual dose:
Max 30 mg/kg/day orally divided every 12 hours (manufacturer recommended) . Continue for a minimum of 48 to 72 hours after patient becomes asymptomatic or bacteria has been eradicated. For infections caused by *Streptococcus pyogenes*, duration of treatment should be at least 10 days. Durations of several weeks may be required for some infections [1]. 100 mg/kg/day orally in 2 divided doses in neonates 2 kg or more [2][3][4][5] and 75 mg/kg/day orally in 2 divided doses in neonates less than 2 kg have been used in infants 0 to 59 days with possible serious infections [3][4][5].

Anthrax[6]
32 to 37 weeks gestational age
0 to 1 week of age: 50 mg/kg/day orally divided every 12 hours
1 to 4 weeks of age: 75 mg/kg/day orally divided every 8 hours
Term newborn
0 to 4 week of age: 75 mg/kg/day orally divided every 8 hours
Duration: For prophylaxis, continue for 60 days after exposure. For naturally acquired cutaneous infection, 7 to 10 days. As follow-up therapy for severe anthrax, complete course for 14 days or longer until clinical criteria for stability are met [6].

Urinary Tract Infection, Prophylaxis: 10 to 15 mg/kg/day orally once daily [7][8].

Dose Adjustments There are no data available for dosing amoxicillin in pediatric patients with renal impairment. In adults, based on the severity of the infection, the lower end of the dose and/or frequency are recommended [1].

Uses

Anthrax, Treatment and Prophylaxis [6]:
Postexposure prophylaxis for *Bacillus anthracis* **(Oral)**
Penicillin-resistant strains or prior to susceptibility testing

- **Preferred:** Ciprofloxacin or doxycycline *Alternatives in order of preference: clindamycin, levofloxacin.*
- **Penicillin-susceptible strains**
- **Preferred:** Amoxicillin *Alternative: penicillin VK.*

Cutaneous Anthrax treatment, without systemic involvement (Oral)
All strains, regardless of penicillin susceptibility or if susceptibility is unknown

- **Preferred:** Ciprofloxacin. *Alternatives in order of preference: doxycycline, clindamycin, levofloxacin.*
- **Alternatives for penicillin-susceptible strains**
- **Preferred:** Amoxicillin *Alternative: penicillin VK.*

Oral follow-up therapy for severe anthrax
Combination Oral Therapy

- **Preferred:** Ciprofloxacin. *Alternative: levofloxacin. If strains are penicillin-susceptible, amoxicillin (preferred) or penicillin VK (alternative).*
- **PLUS**
- **Preferred:** Clindamycin. *Alternatives in order of preference: doxycycline or linezolid.*

Urinary Tract Infection (UTI), Prophylaxis: Some experts recommend amoxicillin prophylaxis starting at birth and continuing until vesicoureteral reflux (VUR) is ruled out in neonates with hydronephrosis [7], though there are no studies in neonates to support prophylaxis.
The use of prophylactic antibiotics for VUR is controversial [11]. When no prophylactic antibiotics were administered, the 2-year rate for recurrent UTI in children (2 months to 71 months of age) was 25.4% and 17.3% with VUR and without VUR, respectively [12]. In children 2 months to 71 months with vesicoureteral reflux, trimethoprim/sulfamethoxazole prophylaxis reduced the risk of infections but did not reduce renal scarring at 2 years [13]; therefore, evidence for routine use of prophylaxis is not established [14].

Pediatric FDA Approved Indications:
For infection caused by β-lactamase-negative organisms only
Ear, nose and throat infections caused by *Streptococcus* species (alpha- and beta-hemolytic strains only), *S pneumoniae*, *Staphylococcus* species, or *Haemophilus influenzae*[1]. For individuals without a penicillin allergy, penicillin or amoxicillin are the agents of choice for the treatment of group A streptococcal pharyngitis [15].

Genitourinary tract infections caused by *Escherichia coli*, *Proteus mirabilis*, or *Enterococcus faecalis*[1].

Skin and skin structure infections caused by *Streptococcus* species (alpha- and beta-hemolytic strains only), *Staphylococcus* species, or *E coli*[1].

Lower respiratory tract infections caused by *Streptococcus* species (alpha- and beta-hemolytic strains only), *S pneumoniae*, *Staphylococcus* species, or *H influenza*[1].

Administration

Suspension: Shake well before measuring the dose; place on tongue for swallowing; may mix the dose with formula, milk, fruit juice, water, ginger ale, or cold drinks; after mixing, administer immediately and completely [9]. May also dissolve amoxicillin powder in breast milk to a concentration of 50 mg/mL [10].

MEDICATION SAFETY

Contraindications/Precautions

Endocrine and metabolic: False positive readings for glucose urine tests may occur with Clinitest(R), Benedict Solution, or Fehling Solution. Use enzymatic glucose oxidase reaction-type tests [1].
Dermatologic: Severe cutaneous adverse reactions (SCAR) such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP) may occur; monitoring recommended and discontinuation may be necessary [16].
Gastrointestinal: Clostridioides difficile-associated diarrhea, including mild diarrhea to fatal colitis, has been reported and may occur over 2 months from last dose. Ongoing antibiotic use not directed against *c difficile* may need to be discontinued [16].
Immunologic: Severe anaphylactic reactions, including fatalities, have been reported, especially in patients with a history of penicillin hypersensitivity or sensitivity to multiple allergens [1].
Mononucleosis: Avoid use due to a high risk of developing an erythematous skin rash [1]
Renal: Severe renal impairment (ie, GFR less than 30 mL/min) or hemodialysis; dose adjustment recommended [1].

Adverse Effects

Common adverse effects include rash, diarrhea, nausea, and vomiting [1].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

An analog of ampicillin, amoxicillin is a semisynthetic antibiotic that inhibits the biosynthesis of the cell wall. It has a broad-spectrum bactericidal activity against most strains of gram-positive and gram-negative microorganisms [1].

Rapidly absorbed, with time to peak concentration of 1 to 2 hours after administration. Widely distributed into most body tissues and fluids, except brain and spinal fluid. May penetrate brain when meninges are inflamed. Protein binding is approximately 20%, and renal excretion is mostly unchanged at approximately 60%. Half-life of immediate-release amoxicillin is 61.3 minutes [1].

Pharmacokinetics- Neonates[17][18][19][20]

Neonates Administered IV Amoxicillin*				
Gestational age (GA) Postnatal age (PNA) Range (mean)	Vd (mean)	Half-life (mean)	Clearance (mean)	Author, year (N)
GA = 25 to 42 weeks (34.6 weeks) PNA = 0 to 9 days (0.76 days)	0.65 L/kg	5.2 hours *	0.096 L/kg/hr	Pullen, 2006 N=150
GA = 26 to 41 weeks (33.7 weeks) PNA = 10 to 52 days (24.7 days)	0.66 L/kg	3 hours *	0.18 L/kg/hr	Pullen, 2007 N=32
GA = 24 to 32 (28.9 weeks) PNA = 1 to 3 days (1.1 day)	0.603 L/kg	6.9 hours * 5.2 hours **	0.061 L/kg/hr * 0.0805 L/hr **	Charles, 1997 N=40
GA = (29 weeks) PNA = (3 days)	0.671 L/kg	6.7 hours **	0.066 L/kg/hr **	Huisman-de boer, 1995 N=17
*Gentamicin coadministered **Gentamicin not coadminsitered				

ABOUT

Special Considerations/Preparation

Availability: Oral suspension (125, 200, 250, or 400 mg/5mL). Also available as chewable tablets (125, 200, 250, and 400 mg), oral capsules (250 or 500 mg), or oral tablets (500 or 875 mg) [1][21][9].
Storage: Store at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F) [1][21][9]
Reconstitution: Tab the bottle until all of the powder flows freely. Add approximately one-third of the total amount of water for reconstitution and shake vigorously. Add remainder of water and shake again [9].

Mixed with Breast Milk

Amoxicillin suspension (50 mg/mL) reconstituted with breast milk was bioequivalent to amoxicillin reconstituted with water in 16 healthy, adult, fasted (10 hours before and 4 hours after dose) volunteers [10].

DOSING/ADMINISTRATION

Dose

Aspergillosis, Invasive
Dosage (alternative therapy): 5 mg/kg IV every 24 hours [1]

Candidiasis, Invasive
Dosage (alternative therapy): 2.5 to 5 mg/kg/dose IV infusion every 24 hours; dose based on a pharmacokinetic study in neonates; optimal regimen for hematogenous *Candida* meningoencephalitis is unknown [2][3].
Duration of Therapy: Use for 2 weeks after documented clearance of *Candida* from the bloodstream and resolution of symptoms [4]. For CNS infection, continue until all signs, symptoms, and CSF and radiological abnormalities have resolved [4][3].

Uses

Treatment of systemic fungal infections resistant to conventional amphotericin B therapy or in patients with renal or hepatic dysfunction.

Neonatal Candidiasis, Including CNS Infection[4]
Invasive candidiasis and candidemia, or very low-birth weight infants with asymptomatic candiduria .

- Amphotericin B deoxycholate is recommended.
- Fluconazole IV or oral is an alternative for those who have not been receiving prophylaxis with fluconazole.
- Lipid formulation amphotericin B agent is an alternative; however, use with caution, especially in the presence of urinary tract involvement.
- Echinocandins (caspofungin, anidulafungin, or micafungin) should be limited to salvage therapy or scenarios of resistance or toxicity to amphotericin B deoxycholate or fluconazole

Central nervous system infections

- Amphotericin B deoxycholate is recommended.
- Liposomal amphotericin B agent is an alternative.
- Salvage therapy with flucytosine may be added in those patients who have not responded to initial therapy.
- Fluconazole may be used as step-down therapy for those patients who respond to initial therapy

Neonatal intensive care unit (with greater than 10% rate of invasive candidiasis)

- Prophylaxis with IV or oral fluconazole for 6 weeks is recommended for neonates with birth weights of less than 1000 g
- Prophylaxis with oral nystatin is an alternative in neonates with birth weights of less than 1500 g when fluconazole is unavailable or fluconazole resistance is present

Infective endocarditis: The following recommendations are based on a consensus of experts [6]. The full pediatric guidelines can be found here: https://doi.org/10.1161/CIR.0000000000000298

Organism Directed Therapy		
Organism	First-Choice	Alternative Choice
Fungi Candida spp, Aspergillus spp	Surgical resection plus Amphotericin B With or without flucytosine	Amphotericin B followed by imidazole (eg, fluconazole, itraconazole, voriconazole) suppression if surgery cannot be performed. Lifelong suppression may be necessary if surgery cannot be performed or relapse occurs after surgery.
Baltimore, 2015		

Administration

Administer by IV infusion over 2 hours (2.5 mg/kg/hour) at a concentration of 1 to 2 mg/mL. If infusion lasts longer than 2 hours, shake the bag to mix the contents every 2 hours. Flush existing IV line with D_5W prior to infusion or administer in a separate IV line. Do not infuse with saline solutions (precipitation will occur). Do not use an in-line filter to administer [5].

MEDICATION SAFETY

Adverse Effects

Anemia, thrombocytopenia, hypokalemia, nausea/vomiting, and fever/chills.

Solution Compatibility

D_5W at 1 to 2 mg/mL dilution.

Solution Incompatibility

NS.

Monitoring

Serum amphotericin B concentrations are not routinely followed. Monitor urine output. Periodic CBC for thrombocytopenia, electrolytes for hypokalemia, BUN, serum creatinine, and hepatic transaminases.
For candidemia, monitor blood cultures daily or every other day until *Candida* is cleared [4].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Amphotericin B lipid complex consists of amphotericin B complexed with two phospholipids in a 1:1 drug-to-lipid ratio. Acts by binding to the sterol component of a cell membrane leading to alterations in the cell wall permeability and death. Penetrates the cell wall of susceptible fungi. Concentrates in the liver and spleen. Less nephrotoxic than conventional amphotericin B. Mean serum half-life in adults 24 to 38 hours. The pharmacokinetics of amphotericin B lipid complex is nonlinear.

ABOUT

Special Considerations/Preparation

Available as a suspension containing 100-mg Abelcet® in 20-mL (5 mg/mL). Shake the vial gently until there is no evidence of any yellow sediment on the bottom. Withdraw the appropriate dose into a syringe using an 18 gauge needle. Remove the needle and replace with the supplied 5 micron filter needle. Dilute the drug with D_5W so that the final infusion concentration is 1 to 2 mg/mL. Shake until thoroughly mixed. Check for complete dispersion. The diluted admixture is stable for 48 hours refrigerated and an additional 6 hours at room temperature [5].
Do not freeze. Protect from light.
Do not flush IV or mix Abelcet® with saline solutions - precipitation willoccur.

Amphotericin B Liposome

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

2.5 to 7 mg/kg/dose every 24 hours IV infusion [1].

Uses

Treatment of systemic fungal infections resistant to conventional amphotericin B therapy or in patients with renal or hepatic dysfunction.

Neonatal Candidiasis, Including CNS Infection[4]
Invasive candidiasis and candidemia, or very low-birth weight infants with asymptomatic candiduria .

- Amphotericin B deoxycholate is recommended.
- Fluconazole IV or oral is an alternative for those who have not been receiving prophylaxis with fluconazole.
- Lipid formulation amphotericin B agent is an alternative; however, use with caution, especially in the presence of urinary tract involvement.
- Echinocandins (caspofungin, anidulafungin, or micafungin) should be limited to salvage therapy or scenarios of resistance or toxicity to amphotericin B deoxycholate or fluconazole

Central nervous system infections

- Amphotericin B deoxycholate is recommended.
- Liposomal amphotericin B agent is an alternative.
- Salvage therapy with flucytosine may be added in those patients who have not responded to initial therapy.
- Fluconazole may be used as step-down therapy for those patients who respond to initial therapy

Neonatal intensive care unit (with greater than 10% rate of invasive candidiasis)

- Prophylaxis with IV or oral fluconazole for 6 weeks is recommended for neonates with birth weights of less than 1000 g
- Prophylaxis with oral nystatin is an alternative in neonates with birth weights of less than 1500 g when fluconazole is unavailable or fluconazole resistance is present

Comparison with Echinocandins: There was no difference in clinical response between

echinocandins and amphotericin B (OR 1.38; 95% CI, 0.68 to 2.8) for the treatment of suspected or confirmed invasive candidiasis in a meta-analysis (n=5; 354 neonates and children). Antifungals included were micafungin, caspofungin, amphotericin B deoxycholate, and liposomal amphotericin B. Subanalysis demonstrated no difference in other comparisons including mycological response, mortality, recurrence of candida infection, type of echinocandin, different risk groups (high-risk, low-risk, or neutropenic groups), and type of use (targeted or empirical). Discontinuation due to adverse effects were higher with amphotericin B than the echinocandins (OR 0.3; 95% CI, 0.12 to 0.76) [5].

Infective endocarditis: The following recommendations are based on a consensus of experts [6]. The full pediatric guidelines can be found here: https://doi.org/10.1161/CIR.0000000000000298

Organism Directed Therapy		
Organism	First-Choice	Alternative Choice
Fungi Candida spp, Aspergillus spp	Surgical resection plus Amphotericin B With or without flucytosine	Amphotericin B followed by imidazole (eg, fluconazole, itraconazole, voriconazole) suppression if surgery cannot be performed. Lifelong suppression may be necessary if surgery cannot be performed or relapse occurs after surgery.
Baltimore, 2015		

Administration

Administer by IV infusion at a concentration of 1 to 2 mg/mL over a period of approximately 60 (if well tolerated) to 120 minutes. To provide sufficient volume for infusion, a final concentration of 0.2 to 0.5 mg/mL may be appropriate for infants and small children [2]. The recommended standard concentrations are 1 or 2 mg/mL [3]. May increase infusion time if patient experiences intolerance during the infusion. Flush existing IV line with D_5W prior to infusion or administer in a separate IV line. In-line filter with pore diameter no less than 1 micron may be used [2].

MEDICATION SAFETY

Contraindications/Precautions

Precautions
Immunologic: Anaphylaxis has been reported; discontinue immediately and do not reinitiate [7].

Adverse Effects

Safety has not been established in pediatric patients younger than 1 month [7].
Common Hypokalemia (37% vs 55%), chills (29% vs 68%), vomiting (27% vs 55%), and hypertension (10% vs 21%) were reported for amphotericin liposome compared with amphotericin B deoxycholate in a double-blind study in 95 children 16 years or younger [7].
Endocrine/Metabolic:
•Hypokalemia occurred at the end of treatment in 21.2% (7 out of 33 pediatric patients) in the liposomal amphotericin B group compared with 28.6% (16 out of 56 pediatric patients) for the conventional amphotericin B group when drugs were administered as recommended (3 to 5 mg/kg/day over at least 1 hour for liposomal and 0.5 to 1.5 mg/kg/day over at least 4 hours for conventional). Potassium replacement therapy was administered to 87.9% of patients in the liposomal amphotericin B group and 89.3% of patients in the conventional group. In those younger than 90 days (n=16), 100% vs 87.5%, respectively, received potassium replacement therapy [8].
Hepatic:
•Hepatotoxicity was more common in pediatric patients who received liposomal amphotericin B compared with conventional amphotericin B in a retrospective study; but when concomitant hepatotoxic drugs were accounted for there was no difference. Additionally, the majority of these children with hepatoxicity had at least 1 enzyme abnormality at baseline. Of 65 pediatric patients with baseline and end-of-treatment liver function test, amphotericin-related hepatotoxicity was 82.8% (24/29) for liposomal amphotericin B and 55.6% (20/36) for conventional amphotericin B (OR 3.8 (1.2 to 12.3; p=0.024)). The LFTs that were different between the 2 groups were gamma-glutamyl transferase (GGT) and bilirubin; GGT was up to 5 x the upper limit of normal (ULN) in 41.4% in the liposomal group compared with 16.7% (p=0.049) in the conventional group and bilirubin was more than 3 to 10 x the ULN in 17.2% and 0%, respectively [8].
Infusion-Related Reactions:
•Infusion-related reactions (rigors, fever, tachycardia, and rash) occurred in 9.1% (3 out of 33 pediatric patients) in the liposomal amphotericin B group compared with 23.2% (13 out of 56 pediatric patients; p=0.15) for the conventional amphotericin B group when drugs were administered as recommended (3 to 5 mg/kg/day over at least 1 hour for liposomal and 0.5 to 1.5 mg/kg/day over at least 4 hours for conventional). None of the reactions occurred in children younger than 90 days (n=16) [8].
Renal:
•Compared with older individuals, pediatric patients appear to have more tolerance for the nephrotoxic effects of amphotericin B deoxycholate [7]. Creatinine elevation (doubling of baseline serum creatinine concentration) occurred in 21.2% (7 out of 33 pediatric patients) in the liposomal amphotericin B group compared with 14.3% (8 out of 56 pediatric patients; p=0.4) for the conventional amphotericin B group when drugs were administered as recommended (3 to 5 mg/kg/day over at least 1 hour for liposomal and 0.5 to 1.5 mg/kg/day over at least 4 hours for conventional). The mean number of concomitant nephrotoxic drugs was 2.5 for the liposomal group compared with 2 for the conventional group [8].

Solution Compatibility

D_5W, $D_{10}W$, $D_{20}W$, $D_{25}W$.

Solution Incompatibility

NS.

Monitoring

Laboratory Exam: Monitor renal function frequently during therapy. Liver function, serum electrolytes (especially magnesium and potassium), and CBC should be assessed regularly during therapy [7].
For candidemia, monitor blood cultures daily or every other day until *Candida* is cleared [4].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

AmBisome® consists of amphotericin B intercalated within a single bilayer liposomal drug delivery system. Acts by binding to the sterol component of a cell membrane leading to alterations in the cell wall permeability and death. Penetrates the cell wall of susceptible fungi. Concentrates in the liver and spleen but penetrates the CNS less than conventional amphotericin B. Less nephrotoxic than conventional amphotericin B. Mean serum half-life in adults 24 to 38 hours. The pharmacokinetics of amphotericin B liposome is nonlinear.

ABOUT

Special Considerations/Preparation

Available as powder for injection in 50 mg vials. Reconstitute by adding 12 mL of sterile water for injection to a yield a concentration of 4 mg/mL. Immediately shake vial vigorously for 30 seconds. Check for complete dispersion. Reconstituted suspension stable for 24 hours refrigerated.

Do not freeze. Protect from light.
Before administration, AmBisome® must be diluted with D_5W to a final concentration less than 2 mg/mL. A 1 mg/mL dilution may be made by filtering (using 5 micron filter) 1 mL of reconstituted solution into 3 mL of D_5W. Use one filter per vial of AmBisome®. Use solution within 6 hours of dilution.
Do not flush IV or mix Ambisome® with saline solutions-precipitation will occur.

Amphotericin B

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Fungal Infections, Suspected or Documented
1 mg/kg every 24 hours IV infusion [1][2][3][4][5]. A dose range of 1 to 1.5 mg/kg/day has been suggested for invasive aspergillosis [6].

Candidiasis, Invasive
1 mg/kg/dose IV every 24 hours for neonates with disseminated candidiasis, including CNS infections [1][2][3][4][5].
Duration of Therapy: Use for 2 weeks after documented clearance of *Candida* from the bloodstream and resolution of symptoms [7]. For CNS infection, continue until all signs, symptoms, and CSF and radiological abnormalities have resolved [7][5]

Uses

Treatment of systemic fungal infections and severe superficial mycoses.

Neonatal Candidiasis, Including CNS Infection[7]
Invasive candidiasis and candidemia, or very low-birth weight infants with asymptomatic candiduria .

- Amphotericin B deoxycholate is recommended.
- Fluconazole IV or oral is an alternative for those who have not been receiving prophylaxis with fluconazole.
- Lipid formulation amphotericin B agent is an alternative; however, use with caution, especially in the presence of urinary tract involvement.
- Echinocandins (caspofungin, anidulafungin, or micafungin) should be limited to salvage therapy or scenarios of resistance or toxicity to amphotericin B deoxycholate or fluconazole

Central nervous system infections

- Amphotericin B deoxycholate is recommended.
- Liposomal amphotericin B agent is an alternative.
- Salvage therapy with flucytosine may be added in those patients who have not responded to initial therapy.
- Fluconazole may be used as step-down therapy for those patients with fluconazole-susceptible isolates who respond to initial therapy

Neonatal intensive care unit (with greater than 10% rate of invasive candidiasis)

- Prophylaxis with IV or oral fluconazole for 6 weeks is recommended for neonates with birth weights of less than 1000 g
- Prophylaxis with oral nystatin is an alternative in neonates with birth weights of less than 1500 g when fluconazole is unavailable or fluconazole resistance is present

Comparison with Echinocandins: There was no difference in clinical response between echinocandins and amphotericin B (OR 1.38; 95% CI, 0.68 to 2.8) for the treatment of suspected or confirmed invasive candidiasis in a meta-analysis (n=5; 354 neonates and children). Antifungals included were micafungin, caspofungin, amphotericin B deoxycholate, and liposomal amphotericin B. Subanalysis demonstrated no difference in other comparisons including mycological response, mortality, recurrence of candida infection, type of echinocandin, different risk groups (high-risk, low-risk, or neutropenic groups), and type of use (targeted or empirical). Discontinuation due to adverse effects were higher with amphotericin B than the echinocandins (OR 0.3; 95% CI, 0.12 to 0.76) [13].

Infective endocarditis: The following recommendations are based on a consensus of experts [14]. The full pediatric guidelines can be found here: https://doi.org/10.1161/CIR.0000000000000298

Organism Directed Therapy		
Organism	First-Choice	Alternative Choice
Fungi Candida spp, Aspergillus spp	Surgical resection plus Amphotericin B With or without flucytosine	Amphotericin B followed by imidazole (eg, fluconazole, itraconazole, voriconazole) suppression if surgery cannot be performed. Lifelong suppression may be necessary if surgery cannot be performed or relapse occurs after surgery.
Baltimore, 2015		

Administration

Infuse over 2 to 6 hours [8][9][10] at a concentration not to exceed 0.1 mg/mL [8]; some institutions have used 0.5 mg/mL concentrations in pediatric patients [11]. Avoid rapid administration (hypotension, hypokalemia, arrhythmias, and shock can occur). **Do not flush IV or mix amphotericin with saline solution; precipitation will occur.** In-line filter with pore diameter no less than 1 micron may be used [8].
To avoid febrile reactions, administration of acetaminophen or diphenhydramine may be considered [12]. Some suggest starting with 0.25 mg/kg/day, followed by increases of 0.25 mg/kg/day until the target dose is reached[4]. However, for patients with severe infections

the dose should be initiated at the target dose [12].

MEDICATION SAFETY

Contraindications/Precautions

Precautions
Administration: Rapid infusion may result in hypotension, hypokalemia, arrhythmias, and shock; infuse over 2 to 6 hours [15].
Administration: If therapy is interrupted for a period longer than 7 days, therapy should be resumed by starting with the lowest dosage level and increased gradually [15].
Infusion Reactions: Acute reactions (fever, shaking, chills, hypotension, anorexia, nausea, vomiting, headache, and tachypnea) are common 1 to 3 hours after initiating infusion. Pretreatment with antipyretics, antihistamines, corticosteroids, or meperidine may improve tolerance to treatment. A single test dose is recommended in some patients to assess tolerance [15].
Neurological: Leukoencephalopathy has occurred; total body irradiation may put patient at risk [15].
Renal: Use with caution in patients with reduced renal function; some patients may need hydration and sodium repletion prior to administration to reduce risk of nephrotoxicity [15].

Adverse Effects

Common Hypokalemia (37% vs 55%), chills (29% vs 68%), vomiting (27% vs 55%), and hypertension (10% vs 21%) were reported for amphotericin liposome compared with amphotericin B deoxycholate in a double-blind study in children 16 years or younger [16]. Other common events with amphotericin B include fever, malaise, weight loss, hypotension, tachypnea, anorexia, nausea, diarrhea, dyspepsia, cramping epigastric pain, anemia (normochromic, normocytic), pain at the injection site with or without phlebitis or thrombophlebitis, generalized pain (including muscle and joint pains), headache, decreased renal function, and renal function abnormalities [15]

Endocrine/Metabolic:
•Hypokalemia (serum K^+ less than 3 mmol/L) occurred in 17% of infants, younger than 30 days of age who received amphotericin B deoxycholate, in the neonatal intensive care unit. The median gestational age was 26 weeks (range, 23 to 41 weeks) and median birth weight was 863 g (range, 546 to 4000 g) [17].
•Hypokalemia occurred at the end of treatment in 21.2% (7 out of 33 pediatric patients) in the liposomal amphotericin B group compared with 28.6% (16 out of 56 pediatric patients) for the conventional amphotericin B group when drugs were administered as recommended (3 to 5 mg/kg/day over at least 1 hour for liposomal and 0.5 to 1.5 mg/kg/day over at least 4 hours for conventional). Potassium replacement therapy was administered to 87.9% of patients in the liposomal amphotericin B group and 89.3% of patients in the conventional group. In those younger than 90 days (n=16), 100% vs 87.5%, respectively, received

potassium replacement therapy [18].

Hepatic:

•Hepatotoxicity was more common in pediatric patients who received liposomal amphotericin B compared with conventional amphotericin B in a retrospective study; but when concomitant hepatotoxic drugs were accounted for there was no difference. Additionally, the majority of these children with hepatoxicity had at least 1 enzyme abnormality at baseline. Of 65 pediatric patients with baseline and end-of-treatment liver function test, amphotericin-related hepatotoxicity was 82.8% (24/29) for liposomal amphotericin B and 55.6% (20/36) for conventional amphotericin B (OR 3.8 (1.2 to 12.3; p=0.024)). The LFTs that were different between the 2 groups were gamma-glutamyl transferase (GGT) and bilirubin; GGT was up to 5 x the upper limit of normal (ULN) in 41.4% in the liposomal group compared with 16.7% (p=0.049) in the conventional group and bilirubin was more than 3 to 10 x the ULN in 17.2% and 0%, respectively [18].

Infusion-Related Reactions:

•Infusion-related reactions (rigors, fever, tachycardia, and rash) occurred in 9.1% (3 out of 33 pediatric patients) in the liposomal amphotericin B group compared with 23.2% (13 out of 56 pediatric patients; p=0.15) for the conventional amphotericin B group when drugs were administered as recommended (3 to 5 mg/kg/day over at least 1 hour for liposomal and 0.5 to 1.5 mg/kg/day over at least 4 hours for conventional). None of the reactions occurred in children younger than 90 days (n=16) [18].

Renal:

•Serum creatinine increased at least 0.4 mg/dL at any time during amphotericin B therapy in 16% (15 out of 92) of infants, 90 days or younger, in the neonatal intensive care unit. None of the values exceeded 2 mg/dL. By the end of therapy, elevated creatinine values normalized in 8 of the 15 infants; 3 had resolving values, and 4 had values that remained elevated. The median gestational age was 26 weeks (range, 23 to 41 weeks) and median birth weight was 863 g (range, 546 to 4000 g). The mean cumulative dose was 13.5 mg/kg and duration was 16.3 days for infants who both developed and did not develop nephrotoxicity; no difference in dose or duration between groups [17].

•Compared with older individuals, pediatric patients appear to have more tolerance for the nephrotoxic effects of amphotericin B deoxycholate [19]. Creatinine elevation (doubling of baseline serum creatinine concentration) occurred in 21.2% (7 out of 33 pediatric patients) in the liposomal amphotericin B group compared with 14.3% (8 out of 56 pediatric patients; p=0.4) for the conventional amphotericin B group when drugs were administered as recommended (3 to 5 mg/kg/day over at least 1 hour for liposomal and 0.5 to 1.5 mg/kg/day over at least 4 hours for conventional). The mean number of concomitant nephrotoxic drugs was 2.5 for the liposomal group compared with 2 for the conventional group [18].

•Sodium intake of more than 4 mEq/kg/day was associated with a decrease in the incidence of amphotericin B-induced nephrotoxicity in extremely premature infants with a birth weight of less than 1250 g [20][21]. Nephrotoxicity developed in 13 out of 21 neonates in the control group compared with 3 out of 16 in the high-sodium intake group (p=0.02). The additional sodium was administered by either increasing the amount of sodium in the total parenteral nutrition (TPN) or normal saline in those who could tolerate excess fluid until sodium could be adjusted in the TPN. All neonates in the high sodium group received 1 mg/kg/day by 2 days of age [21].

Black Box Warning

This drug should be used primarily for treatment of patients with progressive and potentially life-threatening fungal infections; it should not be used to treat noninvasive forms of fungal disease such as oral thrush, vaginal candidiasis and esophageal candidiasis in patients with normal neutrophil counts [15]
The product name and dosage should verified if the prescribed dose exceeds 1.5 mg/kg. Overdose can result in potentially fatal cardiac or cardiorespiratory arrest [15].

Solution Compatibility

D_5W, $D_{10}W$, $D_{15}W$, and $D_{20}W$.

Solution Incompatibility

NS

Terminal Injection Site Compatibility

Amiodarone, heparin, hydrocortisone, sodium bicarbonate, and zidovudine.

Terminal Injection Site Incompatibility

Fat emulsion. Amikacin, aztreonam, calcium chloride, calcium gluconate, cefepime, cimetidine, ciprofloxacin, dopamine, enalaprilat, fluconazole, gentamicin, linezolid, magnesium sulfate, meropenem, penicillin G, piperacillin/tazobactam, potassium chloride, propofol, ranitidine, remifentanil, and tobramycin.

Monitoring

Laboratory Parameters: Monitor renal function frequently during therapy. Liver function, serum electrolytes (especially magnesium and potassium), CBC, and hemoglobin should be assessed regularly during therapy [15].
For candidemia, monitor blood cultures daily or every other day until *Candida* is cleared [7].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of Action: Amphotericin B binds to ergosterol in the membrane of sensitive fungi and may be fungicidal or fungistatic depending on the concentrations achieved in body fluids/tissue [16].

The therapeutic concentration range is not well-defined. Highly protein-bound (greater than 90%). Elimination half-life is approximately 15 days. Drug may accumulate in tissues to a significant concentration and be excreted renally for months [15].

After 5 days of amphotericin B IV in 13 neonates (2 to 55 days of life; mean gestational age 27.4 +/- 5 weeks (24 to 40 weeks)). Dose was increased from 0.1 to 0.5 mg/kg/day over the first 4 to 6 days in 10 infants. The other 3 infants started on 0.8 to 1 mg/kg/day which was reduced to 0.5 mg/kg/day. The mean dose for all patients was 0.54+/-0.16 mg/kg/day. Oral 5-fluorocytosine was started on the same day as amphotericin B [22]
Peak concentration: 0.96 mcg/mL (range 0.5 to 4 mcg/mL) [22]
Vd: 1.5 L/kg (range, 0.1 to 17.5 hours) [22]
CSF Distribution: 40% to 90% of serum (n=5) [22]
Clearance: 18 mL/min/1.73 m^2(range 7.7 to 72.3 mL/min/1.73 m^2) [22]
Half-life: 14.8 hours (range 5 to 82 hours) beta half-life, weeks to months for alpha elimination phase [22]

ABOUT

Special Considerations/Preparation

Available as powder for injection in 50-mg vials. **Protect the vials from light**. Reconstitute with 10 mL of D_5W or preservative free sterile water to a concentration of 5 mg/mL, then dilute further using D_5W to a concentration no greater than 0.1 mg/mL for infusion. Reconstituted solution stable for 24 hours at room temperature or 7 days in refrigerator. **Do not flush IV or mix amphotericin with saline solution; precipitation will occur.** May filter if necessary; mean pore diameter should not be less than 1 micron. The manufacturer recommends protecting the solution from light during administration [8]. However, there are available data that demonstrate protection from light to be unnecessary in typical hospital lighting if administered within 24 hours of preparation [23].

Intravitreal injection: amphotericin B deoxycholate 5 to 10 mcg/0.1 mL of sterile water [7].

DOSING/ADMINISTRATION

Dose

General Dosage (see below for specific indications)
25 to 50 mg/kg/dose [1][2] by IV slow push, or IM.
Renal function and drug elimination are most strongly correlated with postmenstrual age (PMA; equivalent to gestational age plus postnatal age). PMA is the primary determinant of dosing interval, with postnatal age as the secondary qualifier.

Dosing Interval Chart		
PMA (weeks)	**PostNatal (days)**	**Interval (hours)**
≤29	0 to 28 >28	12 8
30 to 36	0 to 14 >14	12 8
37 to 44	0 to 7 >7	12 8
≥45	ALL	6

Anthrax[3]
32 up to 34 weeks gestational age
0 to 1 week: 50 mg/kg/dose IV every 12 hours
1 to 4 weeks: 50 mg/kg/dose IV every 8 hours
34 weeks gestational age or older
0 to 1 week: 50 mg/kg/dose IV every 8 hours
1 to 4 weeks: 50 mg/kg/dose IV every 6 hours
Duration: 2 to 3 weeks or more until stable. Continue antimicrobial course of prophylaxis (usually oral therapy) for up to 60 days from onset of illness [3].

Bacteremia, Group B Streptococcal Disease; Empiric and Definitive Therapy (Early- and late-onset) [4]
Guideline Dosage

Gestational Age	Postnatal age		Duration
	7 days or younger†	Older than 7 days‡	
34 weeks or less	50 mg/kg/dose IV every 12 hours	75 mg/kg/dose IV every 12 hours	10 days for bacteremia without a focus; longer durations

Greater than 34 weeks	50 mg/kg/dose IV every 8 hours	50 mg/kg/dose IV every 8 hours	may be necessary for prolonged or complicated courses.
† Use with an aminoglycoside for empirical therapy in full-term newborns 7 days or younger. ‡ Use with ceftazidime for empirical therapy for previously healthy infants, 8 to 28 days of age, in the community when critical illness and meningitis are absent.			
Puopolo, 2019			

Bacteremia (Septicemia)
FDA Dosage[5]

Gestational Age	Postnatal Age		Duration
	7 days or younger	8 days to younger than 28 days	Continue for a minimum of 48 to 72 hours after asymptomatic or evidence of bacterial eradication. For group A beta-hemolytic streptococci, treat for at least 10 days.
34 weeks or less	50 mg/kg/dose IV every 12 hours	75 mg/kg/dose IV every 12 hour	
Greater than 34 weeks	28 days or younger		
	50 mg/kg/dose IV every 8 hours		
Product Information, 2017			

Meningitis, Group B Streptococcal Disease; Empiric and Definitive Therapy (Early- and late-onset) [4]
Guideline Dosage

Postnatal age	Dosage	Duration
7 days or younger†	100 mg/kg/dose IV every 8 hours	14 days for uncomplicated meningitis; longer durations may be necessary for prolonged or complicated courses.
Older than 7 days	75 mg/kg/dose IV every 6 hours	
† Use with an aminoglycoside for empirical therapy in full-term newborns 7 days or younger. ‡ Use with ceftazidime and vancomycin for		

empirical therapy for previously healthy infants, 8 to 90 days of age.
Puopolo, 2019

Meningitis, Bacterial
FDA Dosage[5]

<table>
<tr><td rowspan="2">Gestational Age</td><td colspan="2">Postnatal Age</td><td>Duration</td></tr>
<tr><td>7 days or younger</td><td>8 days to younger than 28 days</td><td rowspan="4">Continue for a minimum of 48 to 72 hours after asymptomatic or evidence of bacterial eradication. For group A beta-hemolytic streptococci, treat for at least 10 days.</td></tr>
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<tr><td colspan="2">50 mg/kg/dose IV every 8 hours</td></tr>
<tr><td colspan="4">Product Information, 2017</td></tr>
</table>

Uses

Broad-spectrum antibiotic useful against group B *streptococcus, Listeria monocytogenes,* and susceptible *E coli* species.

Anthrax[3]:

Systemic Anthrax when meningitis can be ruled out (IV)
Combination IV Therapy

- **Preferred:** Ciprofloxacin. *Alternatives in order of preference: meropenem, levofloxacin, imipenem/cilastatin, or vancomycin. If strains are penicillin-susceptible, then penicillin G (preferred) or ampicillin (alternative).*
- **Plus**
- **Preferred:** Clindamycin. *Alternatives in order of preference: linezolid, doxycycline (not for neonates 37 weeks gestation or younger), or rifampin.*

Systemic Anthrax (meningitis or disseminated infection and meningitis cannot be ruled out) (IV)
Triple IV Therapy

- **Preferred:** Ciprofloxacin. *Alternatives in order of preference: levofloxacin or moxifloxacin*
- **Plus**

- **Preferred:** Meropenem. *Alternatives in order of preference: imipenem/cilastatin or doripenem. If strains are penicillin-susceptible, then penicillin G (preferred) or ampicillin (alternative).*
- **Plus**
- **Preferred:** Linezolid. *Alternatives in order of preference: clindamycin or rifampin or as a last resort, chloramphenicol*

Group B Streptococcal (GBS) Disease:
Definitive
The preferred antibiotic for early-onset and late-onset, culture confirmed-GBS disease is penicillin G and the alternative is ampicillin [4].
Empiric
Preterm infants: The choice is based on multiple factors in those continuously hospitalized beyond 72 hours of age. Empirical choices include group B streptococci-susceptible antibiotics including a β-lactam, cephalosporin, or vancomycin [4].
7 days or younger: The preferred empiric therapy is ampicillin plus an aminoglycoside. If there is compelling reason to suspect an ampicillin-resistant infection in a critically ill neonate, especially very-low-birth-weight neonates, then consider the addition of a broader-spectrum antibiotic [4].
8 to 28 days: Ampicillin plus ceftazidime is preferred for previously healthy infants in the community when critical illness and meningitis are absent [4].
29 to 90 days: Ceftriaxone is recommended for critically ill infants with meningitis [4].
8 to 90 days: Adding vancomycin to empiric therapy is recommended for previously healthy infants in the community if there is evidence of meningitis or critical illness to expand coverage, including for β-lactam-resistant *Streptococcus pneumoniae*[4].

Infective endocarditis: The following recommendations are based on a consensus of experts [8]. The full pediatric guidelines can be found here: https://doi.org/10.1161/CIR.0000000000000298

Organism Directed Therapy		
Organism	First-Choice	Alternative Choice
Streptococci		
Highly susceptible to penicillin G (MBC 0.1 mcg/mL or less); includes most viridans streptococci, groups A, B, C, G nonenterococcal, group D streptococci (S bovis, S equinus)	Penicillin G or CefTRIAXone	Vancomycin or First-generation cephalosporin or CefTRIAXone
Relatively resistant to penicillin (MBC 0.2 mcg/mL or	Penicillin G or Ampicillin + Gentamicin (for first 2	Vancomycin + Gentamicin for enterococci Ampicillin +

more); less-susceptible viridans streptococci or enterococci	weeks, or entire course for enterococci)	CefTRIAXone (for aminoglycoside (AMG)-resistant enterococci or AMG-intolerant patient) CefTRIAXone + gentamicin (not for enterococcal endocarditis)
Resistant to penicillin	Consult an infectious disease specialist.	---
Staphylococci (S aureus or coagulase-negative staphylococci) †		
Penicillin G susceptible (1 mcg/mL or less) (rare)	Penicillin G	Oxacillin or Nafcillin or First-generation cephalosporin or Vancomycin
Penicillin G resistant (0.1 mcg/mL)	Oxacillin or Nafcillin with or without Gentamicin	Vancomycin (for those highly allergic to beta-lactam antibiotics) or First-generation cephalosporin
Oxacillin (MRSA) resistant (4 mcg/mL)	Vancomycin	Daptomycin for right-sided endocarditis, maybe for left-sided
Vancomycin resistant or intolerant	Daptomycin	Unknown
	†When prosthetic material present add riFAMpin + gentamicin (for first 2 weeks) for all staphylococci	
Gram-negative enteric bacilli	CefTAZidime or Cefepime or Cefotaxime or CefTRIAXone Plus	Broad-spectrum penicillin Plus gentamicin (or tobramycin or amikacin)

	gentamicin (or tobramycin or amikacin, depending on susceptibility)	
HACEK group	CefTRIAXone or Cefotaxime or Ampicillin-sulbactam	Ampicillin (when susceptible) Plus aminoglycoside
KEY: AMG = aminoglycosides; HACEK = Haemophilus species, Aggregatibacter species, Cardiobacterium hominis, Eikenella corrodens, and Kingella species; MBC = minimum bactericidal concentration, MRSA = methicillin-resistant Staphylococcus aureus (includes resistance to oxacillin, nafcillin, and cephalosporins)		
Baltimore, 2015		

Meningitis: Empiric agents for the treatment of meningitis in neonates are ampicillin, gentamicin, and cefotaxime [9]. Reassess therapy based on culture and sensitivity results [10].

Sepsis, Early-Onset

Ampicillin plus gentamicin are the agents of choice for empirical treatment of early-onset sepsis (EOS) in neonates at most risk for EOS. Broad-spectrum antibiotics may be necessary in neonates who are severely ill, particularly preterm neonates at high risk for EOS after prolonged antepartum maternal antibiotic treatment [11][12].

Gestational age 34 6/7 weeks or younger

Highest risk for EOS: Administer empirical antibiotics in those at highest risk; neonates born preterm because of maternal cervical incompetence, preterm labor, premature rupture of membranes, clinical concern for intraamniotic infection, or acute onset of unexplained nonreassuring fetal status [11]

Low risk: Consider empirical antibiotics based on the risks and benefits. Those at low risk are those born preterm by cesarean delivery because of maternal noninfectious illness or placental insufficiency in the absence of labor, attempts to induce labor, or rupture of membranes before delivery [11]

Gestational age 35 0/7 weeks or older: Administer empirical antibiotics based on level of risk. Multiple approaches of determining risk may be used including categorical algorithms, multivariate risk assessments, or serial physical examinations [12].

Duration:

•Discontinue antibiotics by 36 to 48 hours when blood cultures are sterile, unless a site-specific infection has been identified, for preterm and full term neonates [11][12].

•Procalcitonin values in addition to perinatal risk factors, signs and symptoms, and laboratory values may aid in the determination to discontinue antibiotic therapy in neonates with suspected early-onset sepsis. The duration of antibiotic therapy was reduced by 9.9 hours with a procalcitonin-guided algorithm compared with standard care in a multicenter randomized control trial of 1710 neonates born after 34 weeks of gestational age with possible or unlikely sepsis. Re-infection and mortality was not different between the groups

(risk difference 0.1% (95% CI, -5.2% to 5.3%) [13].

Pediatric FDA Approved Indications

•Bacterial meningitis caused by *E coli*, group B streptococci, and other gram-negative bacteria (*Listeria monocytogenes*, *N meningitides*). Addition of an aminoglycoside may increase effectiveness against gram-negative bacteria [5].

•Septicemia caused by susceptible gram-positive organisms including *Streptococcus* species, penicillin G-susceptible staphylococci, and enterococci. Gram-negative sepsis caused by *E coli*, *P mirabilis* and *Salmonella* species. Addition of an aminoglycoside may enhance effectiveness [5].

Administration

Intravenous
Doses 500 mg or less should be administered slowly over 3 to 5 minutes IV and over at least 10 to 15 minutes for doses 1 g or greater [6]. Recommended concentrations are 30, 40, 50, and 100 mg/mL for intermittent IV [7].
Intramuscular
Mix to a final concentration of 250 mg/mL for IM administration [6].

MEDICATION SAFETY

Adverse Effects

Very large doses may result in CNS excitation or seizure activity. Moderate prolongation of bleeding times (by approximately 60 seconds) has been reported after the third or fourth dose in neonates 33 to 41 weeks GA receiving 50 to 100 mg/kg every 12 hours[15]. Prolongation of bleeding times (by approximately 2 minutes) has also been reported after at least 10 doses in preterm very low birth-weight neonates 23 to 30 weeks GA receiving 50 to 100 mg/kg every 12 hours [16]. The clinical implications of the prolonged bleeding time is unknown. Hypersensitivity reactions (maculopapular rash, urticarial rash, or fever) are rare in neonates.

Solution Compatibility

D_5W, D_5W in 0.45% sodium chloride, lactated ringer's solution, NS, sterile water.
Stability is dependent on storage temperature and duration, and concentration of ampicillin[6].

Solution Incompatibility

$D_{10}W$, D_5NS, D_5W in 0.45% sodium chloride (Trissel's 2 Clinical Pharmaceutics Database). Ampicillin may be compatible with D_5W in 0.45% sodium chloride, *depending upon storage temperature and duration, and concentration of ampicillin*[6]

Terminal Injection Site Compatibility

Acyclovir, alprostadil, aminophylline, aztreonam, calcium gluconate, cefepime, chloramphenicol, cimetidine, clindamycin, enalaprilat, famotidine, furosemide, heparin, hydrocortisone succinate, insulin, lidocaine, linezolid, magnesium sulfate, metronidazole, milrinone, morphine, phytonadione, potassium chloride, propofol, ranitidine, remifentanil, and vancomycin.

Terminal Injection Site Incompatibility

Amikacin, amiodarone, dopamine, epinephrine, erythromycin lactobionate, fluconazole, gentamicin, hydralazine, metoclopramide, midazolam, nicardipine, sodium bicarbonate, and tobramycin.
Ampicillin 100 mg/mL: TPN formulas with TrophAmine 2% and TrophAmine 3%

Monitoring

•Periodic assessment of renal, hepatic, and hematopoietic function in patients receiving extended treatment [14].
•After 2 consecutive procalcitonin measurements within the normal range and when there is a low risk for infection (assessed by perinatal risk factors, clinical symptoms, and other laboratory findings), consider discontinuation of antibiotics for suspected early-onset sepsis in neonates (34 weeks or older) categorized as infection possible or unlikely. All neonates should receive a minimum of 24 hours of antibiotics before discontinuation [13].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Ampicillin is a semisynthetic penicillin that is bactericidal. Clearance is primarily by the renal

route and is inversely related to postnatal age. Serum half-life in term infants younger than 7 days is approximately 4 hours.

Population pharmacokinetic parameters were determined in a multicenter trial [17]:

Pharmacokinetic Parameters				
Gestational Age	Postnatal Age	Clearance*	Volume*	Half-life*
34 weeks or less	7 days or less (n=21)	0.055 (0.03 to 0.07) L/hr/kg	0.4 (0.4 to 0.4) L/kg	5 (3.9 to 9.4) hours
	8 to 28 days (n=7)	0.07 (0.03 to 0.07) L/hr/kg	0.4 (0.4 to 0.41) L/kg	4 (3.8 to 8.3) hours
Greater than 34 weeks	7 days or less (n=27)	0.086 (0.04 to 0.13) L/hr/kg	0.4 (0.4 to 0.4) L/kg	3.2 (2.2 to 6.2) hours
	8 to 28 days (n=18)	0.11 (0.06 to 0.13) L/hr/kg	0.4 (0.4 to 0.41) L/kg	2.4 (2.1 to 4.7) hours
*median (ranges)				

Controlled Hypothermia
Pharmacokinetic Parameters: The mean (+/-SD) pharmacokinetic parameters in 13 neonates (median gestational age 39 weeks and mean estimated glomerular filtration rate of 43 mL/min/1.73^2) with hypoxic-ischemic encephalopathy undergoing controlled hypothermia were 0.43+/-0.12 mL/min/kg for total body clearance, 0.35+/-0.46 L/kg for volume of the central compartment, and 0.52+/-0.28 L/kg for total volume of distribution [18].
Potential Dosage: Doses of 25 mg/kg or 50 mg/kg IV every 24 hours achieved optimal trough concentrations in dose simulations using gestational age of 36 to 41 weeks, estimated creatinine clearance of 27 to 76 mL/min/1.73^2, and weight of 2.4 to 4.85 kg (mimicking neonates with hypoxic-ischemic encephalopathy undergoing controlled hypothermia). Steady state trough concentrations remained above an MIC of 8 mcg/mL for 100% of the dosing interval with a probability of at least 94% [18].

ABOUT

Special Considerations/Preparation

Available as powder for injection in 125-, 250-, 500-mg, 1-g, 2-g, and 10-g vials.

Reconstitute using sterile water for injection. **Maximum concentration for IV infusion is 100 mg/mL.** Mix to a final concentration of 250 mg/mL for IM administration. **Reconstituted solution must be used within 1 hour of mixing because of loss of potency**.

Anidulafungin

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Candidiasis
Full term infants when intolerant to or resistant to fluconazole or amphotericin B
Loading dose: 3 mg/kg IV for 1 dose [1][2]. A higher dose may be required in patients receiving extracorporeal membrane oxygenation (ECMO) [1].
Maintenance dose: 1.5 mg/kg IV once daily [1][2]. Higher doses may be required in patients receiving extracorporeal membrane oxygenation (ECMO) [1]. Duration of therapy for candidemia, without metastatic complications, is 2 weeks after documented clearance of *Candida* from the bloodstream and resolution of symptoms [3].

Uses

Neonatal Candidiasis, Including CNS Infection[3]
Invasive candidiasis and candidemia, or very low-birth weight infants with asymptomatic candiduria .

- Amphotericin B deoxycholate is recommended.
- Fluconazole IV or oral is an alternative for those who have not been receiving prophylaxis with fluconazole.
- Lipid formulation amphotericin B agent is an alternative; however, use with caution, especially in the presence of urinary tract involvement.
- Echinocandins (caspofungin, anidulafungin, or micafungin) should be limited to salvage therapy or scenarios of resistance or toxicity to amphotericin B deoxycholate or fluconazole

Central nervous system infections

- Amphotericin B deoxycholate is recommended.
- Liposomal amphotericin B agent is an alternative.
- Salvage therapy with flucytosine may be added in those patients who have not responded to initial therapy.
- Fluconazole may be used as step-down therapy for those patients who respond to initial therapy

Neonatal intensive care unit (with greater than 10% rate of invasive candidiasis)

- Prophylaxis with IV or oral fluconazole for 6 weeks is recommended for neonates with birth weights of less than 1000 g
- Prophylaxis with oral nystatin is an alternative in neonates with birth weights of less

than 1500 g when fluconazole is unavailable or fluconazole resistance is present

In a safety and pharmacokinetic study, doses of 1.5 mg/kg/day for 5 days in 8 neonates (6 out of 8 preterm) provided similar anidulafungin exposures compared to children and adults (100 mg/day) [1]. Despite sensitivity to amphotericin B, fungal peritonitis was not cleared in a full-term neonate until anidulafungin was added to liposomal amphotericin B; *Candida albicans* had been cultured from the peritoneum while the patient was receiving amphotericin B monotherapy [2]. Doses for hematogenous *Candida* meningoencephalitis (HCME) are expected to be much higher than those used for other indications, based upon a translational study which used neonatal (6 out of 8 were preterm) pharmacokinetic data applied to an animal model of the disease [5].

FDA Approved Indications

Treatment of candidemia and intra-abdominal abscess and peritonitis due to *Candida* in patients 1 month or older [4]..

Limitations of Use

Anidulafungin has not been studied in adult and pediatric patients with endocarditis, osteomyelitis, and meningitis due to Candida, and has not been studied in sufficient numbers of neutropenic patients to determine efficacy in this group. The dosage of anidulafungin for the treatment of Candida dissemination into the CNS and the eye has not been established [4].

Anidulafungin is associated with high relapse rates in esophageal candidiasis [4]

Administration

Administer by IV Infusion [4]over 60 minutes [1]; not to exceed 1.1 mg/minute (equivalent to 1.4 mL/min or 84 mL/hr) [4].

MEDICATION SAFETY

Contraindications/Precautions

Contraindications

Hypersensitivity to other echinocandins [4].

Known or suspected Hereditary Fructose Intolerance (HFI) [4]

Precautions

Hepatic: Liver function test abnormalities have been reported. Hepatitis, hepatic failure, and significant hepatic dysfunction occurred in patients with underlying medical conditions receiving multiple concomitant medications; monitoring recommended [4]

Immunologic: Anaphylactic reactions, including shock, have been reported; discontinue use [4]

Immunologic: Infusion-related reactions (eg rash, urticaria, flushing, pruritus, bronchospasm, dyspnea, and hypotension) have been reported; dosage adjustment

recommended [4]
Low-birth-weight infants: Contains polysorbate 80; risk of toxicity, including thrombocytopenia, renal dysfunction, hepatomegaly, cholestasis, ascites, hypotension, and metabolic acidosis in low-birth weight infants receiving high doses of polysorbate (unapproved use) [4]
Special population: Contains fructose; metabolic crisis, including life-threatening hypoglycemia, hypophosphatemia, lactic acidosis, and hepatic failure may occur in patients with hereditary fructose intolerance (HFI). Obtain history of HFI symptoms with fructose/sucrose exposure prior to treatment initiation [4]

Adverse Effects

Adverse events reported were hypotension (1), adrenal insufficiency (1), abnormal X-ray of kidneys, ureter, and bladder (1), death (1), infection (1), pulmonary edema (1), and oliguria or uremia (2) in a safety study of 8 neonates [1].

Solution Compatibility

D_5W, NS.

Terminal Injection Site Compatibility

Anidulafungin 0.5 mg/mL
Acyclovir (7 mg/mL), amikacin (5 mg/mL), aminocaproic acid (50 mg/mL), aminophylline (2.5 mg/mL), amiodarone (4 mg/mL), amphotericin B lipid complex (1 mg/mL), amphotericin B liposome (1 mg/mL), ampicillin (20 mg/mL), ampicillin/sulbactam (20 and 10 mg/mL), argatroban (1 mg/mL), atracurium (0.5 mg/mL), azithromycin (2 mg/mL), aztreonam (40 mg/mL), bivalirudin (5 mg/mL), bumetanide (40 mcg/mL), calcium chloride (40 mg/mL), calcium gluconate (40 mg/mL), caspofungin (0.5 mg/mL), cefazolin (20 mg/mL), cefepime (20 mg/mL), cefotaxime (20 mg/mL), cefotetan (20 mg/mL), cefoxitin (20 mg/mL), ceftazidime (40 mg/mL), ceftriaxone (20 mg/mL), cefuroxime (30 mg/mL), chloramphenicol (20 mg/mL), cimetidine (12 mg/mL), ciprofloxacin (2 mg/mL), cisatracurium (0.5 mg/mL), clindamycin (10 mg/mL), cyclosporine (5 mg/mL), dexamethasone (1 mg/mL), dexmedetomidine (4 mcg/mL), digoxin (0.25 mg/mL), diltiazem (5 mg/mL), diphenhydramine (2 mg/mL), dobutamine (4 mg/mL), dolasetron (2 mg/mL), dopamine (3.2 mg/mL), doxycycline hyclate (1 mg/mL), enalaprilat (0.1 mg/mL), epinephrine (50 mcg/mL), erythromycin (5 mg/mL), esmolol (10 mg/mL), famotidine (2 mg/mL), fentanyl (50 mcg/mL), fluconazole (2 mg/mL), foscarnet (24 mg/mL), fosphenytoin (20 mgPE/mL), furosemide (3 mg/mL), ganciclovir (20 mg/mL), gentamicin (5 mg/mL), glycopyrrolate (0.2 mg/mL), granisetron (50 mcg/mL), haloperidol (0.2 mg/mL), heparin (100 units/mL), hydralazine (1 mg/mL), hydrocortisone (1 mg/mL), hydromorphone (0.5 mg/mL), imipenem/cilastatin (5 mg/mL), insulin (1 unit/mL), isoproterenol (20 mcg/mL), ketorolac (15 mg/mL), labetalol (2

mg/mL), levofloxacin (5 mg/mL), lidocaine (10 mg/mL), linezolid (2 mg/mL), lorazepam (0.5 mg/mL), mannitol (150 mg/mL; 15%), meropenem (2.5 mg/mL), methotrexate (12.5 mg/mL), methyldopate (10 mg/mL), methylprednisolone (5 mg/mL), metoclopramide (5 mg/mL), metronidazole (5 mg/mL), midazolam (1 mg/mL), milrinone (0.2 mg/mL), morphine (15 mg/mL), moxifloxacin (1.6 mg/mL), mycophenolate mofetil (6 mg/mL), nafcillin (20 mg/mL), naloxone (0.4 mg/mL), nicardipine (1 mg/mL), nitroglycerin (0.4 mg/mL), nitroprusside (2 mg/mL), norepinephrine (0.12 mg/mL), octreotide (5 mcg/mL), ondansetron (1 mg/mL), palonosetron (50 mcg/mL), pancuronium (0.1 mg/mL), pantoprazole (0.4 mg/mL), pentobarbital (5 mg/mL), phenobarbital (5 mg/mL), phenylephrine (1 mg/mL), piperacillin/tazobactam (40 and 5 mg/mL), potassium chloride (0.1 mEq/mL), procainamide (20 mg/mL), propranolol (1 mg/mL), quinupristin/dalfopristin (5 mg/mL), ranitidine (2 mg/mL), rocuronium (1 mg/mL), succinylcholine (2 mg/mL), sulfamethoxazole-trimethoprim (4 and 0.8 mg/mL), tacrolimus (20 mcg/mL), ticarcillin/clavulanate (31 mg/mL), tobramycin (5 mg/mL), vancomycin (10 mg/mL), vasopressin (1 unit/mL), vecuronium (1 mg/mL), verapamil (2.5 mg/mL), voriconazole (4 mg/mL), zidovudine (4 mg/mL).

Terminal Injection Site Incompatibility

Amphotericin B conventional colloidal, diazepam, ertapenem, magnesium sulfate, nalbuphine, phenytoin, sodium bicarbonate.

Compatibility information refers to physical compatibility and is derived from Trissel's™ 2 Clinical Pharmaceutics Database. The determination of compatibility is based on concentrations for administration recommended herein. Drug compatibility is dependent on multiple factors (eg, drug concentrations, diluents, storage conditions). This list should not be viewed as all-inclusive and should not replace sound clinical judgment. The user is referred to Trissel's™ 2 for more complete details.
Trissel's™ 2 Clinical Pharmaceutics Database, version updated on 06/15/2012.

Monitoring

Therapeutic Laboratory Monitoring

•For candidemia, monitor blood cultures daily or every other day until *Candida* is cleared [3]. Prior to initiation, obtain specimens for fungal culture and other relevant laboratory studies (including histopathology) [4].

Toxic Laboratory Monitoring

Monitor liver function tests [4].

Toxic Physical Monitoring

Monitor for signs and symptoms of worsening hepatic function in patients who develop abnormal liver function tests during therapy [4]

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Anidulafungin, a semi-synthetic echinocandin, is a non-competitive inhibitor of beta-(1,3)-D-glucan synthase; this enzyme is responsible for formation of the polysaccharide, beta-(1,3)-glucan, an essential fungal cell wall component [6]. Anidulafungin is most active (MIC_{90} in mcg/mL) against *Candida albicans* (0.06), *C glabrata* (0.12), *C tropicalis* (0.06), and *C krusei* (0.12) isolates, but less potent against *C parapsilosis* (2) and *C guilliermondii* (2). It has demonstrated activity against the biofilms of *C. albicans* and *C. parapsilosis*. The minimum effective concentration $_{90}$ against *Aspergillus fumigatus* is 0.008 mcg/mL [7]. *Candida* isolates with reduced susceptibility to anidulafungin have been reported. The clinical relevance of these reports is unknown, but the development of drug resistance may be possible. Extensively bound to plasma proteins (greater than 99%). No hepatic metabolism; not a substrate, inducer, or inhibitor of CYP450. Undergoes slow chemical degradation at physiologic temperature and pH to a ring-opened peptide (inactive). In a single-dose study, less than 1% was recovered in urine and approximately 30% was recovered in the feces over 9 days, of which less than 10% was intact anidulafungin. Not removed by hemodialysis [6].

In a pharmacokinetic and safety study following 3 to 5 days of anidulafungin (n=15; age 2 days to 2 years), neonates (n=8; 6 out of 8 premature) demonstrated a median weight adjusted clearance of 0.02 L/kg/hr (range 0.013 to 0.049), median half-life of 78 hours (range 40 to 219), and median exposure of 74.9 mcg*hr/mL (30.4 to 108.9). The lowest exposure was seen in 2 neonates who received extracorporeal membrane oxygenation (ECMO), a process which may alter volume of distribution and/or clearance, and therefore drug exposure. The inclusion of data from the ECMO patients in the calculations likely skewed the median pharmacokinetic values for the entire neonatal study population [1].

ABOUT

Special Considerations/Preparation

Availability: 50-mg and 100-mg single-use vials of anidulafungin lyophilized powder for solution. The 50-mg and 100-mg vials also contain fructose (50 mg and 100 mg, respectively) and mannitol (250 mg and 500 mg, respectively) [6].

Storage

Store powder in the refrigerator between 2 and 8 degrees C (36 and 46 degrees F); do not freeze. Excursions for 96 hours up to 25 degrees C (77 degrees F) are permitted, and the vial can be returned to storage between 2 and 8 degrees C (36 and 46 degrees F) [4].

Store reconstituted solution at a temperature up to 25 degrees C (77 degrees F) for up to 24 hours [4].

Store diluted solution at a temperature up to 25 degrees C (77 degrees F) for up to 48 hours; do not freeze [4].

Preparation

Reconstitute with Sterile Water for Injection only. After reconstitution, drug should be further diluted in D_5W or NS only; do not dilute with other solutions or co-infuse with other medications or electrolytes [4].
Reconstitute 50-mg vial with 15 mL SWFI, and reconstitute 100-mg vial with 30 mL SWFI; concentration of reconstituted vials is 3.33 mg/mL [4].
Doses 50 mg or greater: Final concentrations are 0.77 mg/mL. For 50 mg dose, further dilute the reconstituted contents of the 50-mg vial with 50 mL solution (total volume, 65 mL); for 100 mg dose, further dilute the reconstituted contents of 100-mg vial (or two 50 mg vials) with 100 mL solution (total volume, 130 mL); for 200 mg dose, further dilute the reconstiuted contents of two 100 mg vials (or four 50 mg vials) with 200 mL solution (total volume, 260 mL). [4].
Doses below 50 mg:
• First, calculate the volume (mL) of reconstituted anidulafungin required; volume of reconstituted anidulafungin (mL) = dose of anidulafungin (mg) divided by 3.33 mg/mL [4].
• Then, calculate the total volume of the infusion solution (mL) that contains a final concentration of 0.77 mg/mL; total volume of infusion solution (mL) = dose of anidulafungin (mg) divided by 0.77 mg/mL [4].
• Then, calculate the volume of diluent required to prepare the infusion solution; volume of diluent (mL) = total volume of final infusion solution (mL) minus the volume of reconstituted anidulafungin (mL) [4].

Arginine

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Acute Hyperammonemia - Urea Cycle Disorders
Pending Definitive Diagnosis of Urea Cycle Enzyme Deficiency:
Premedication for loading dose: Ondansetron 0.15 mg/kg IV [1]
Loading dose: Arginine hydrochloride 600 mg/kg in combination with sodium phenylacetate 250 mg/kg and sodium benzoate 250 mg/kg as an IV infusion over 90 to 120 minutes [2][3][4][5].
Maintenance dose: Arginine hydrochloride 600 mg/kg in combination with sodium phenylacetate 250 mg/kg and sodium benzoate 250 mg/kg as an IV infusion over 24 hours [2][3][4][5].
Alternative dose: 250 to 400 mg/kg IV bolus in combination with sodium phenylacetate 250 mg/kg and sodium benzoate 250 mg/kg IV bolus over 90 to 120 minutes, followed by maintenance infusions of arginine 250 mg/kg/day in combination with sodium phenylacetate 250 to 500 mg/kg/day and sodium benzoate 250 to 500 mg/kg/day. **Maximum arginine dose 12 g/day, sodium phenylacetate 12 g/day and sodium benzoate 12 g/day** [1]

Known CPS, OTC, or NAGS Deficiency:
Premedication for loading dose: Ondansetron 0.15 mg/kg IV [1]
Loading dose: Arginine hydrochloride 200 mg/kg in combination with sodium phenylacetate 250 mg/kg and sodium benzoate 250 mg/kg as an IV infusion over 90 to 120 minutes [2][3][6][4][5].
Maintenance dose: Arginine hydrochloride 200 mg/kg in combination with sodium phenylacetate 250 mg/kg and sodium benzoate 250 mg/kg as an IV infusion over 24 hours [2][3][6][4][5].
Alternative dose: 250 mg/kg IV bolus in combination with sodium phenylacetate 250 mg/kg and sodium benzoate 250 mg/kg IV bolus over 90 to 120 minutes, followed by maintenance infusions of arginine 250 mg/kg/day in combination with sodium phenylacetate 250 to 500 mg/kg/day and sodium benzoate 250 to 500 mg/kg/day. **Maximum arginine dose 12 g/day, sodium phenylacetate 12 g/day and sodium benzoate 12 g/day** [1]

Known ASS or ASL Deficiency:
Premedication for loading dose: Ondansetron 0.15 mg/kg IV [1]
Loading dose: Arginine hydrochloride 600 mg/kg in combination with sodium phenylacetate 250 mg/kg and sodium benzoate 250 mg/kg as an IV infusion over 90 to 120 minutes [2][3][6][4][5].
Maintenance dose: Arginine hydrochloride 600 mg/kg in combination with sodium phenylacetate 250 mg/kg and sodium benzoate 250 mg/kg as an IV infusion over 24 hours [2][3][6][4][5].
Alternative dose (ASS Deficiency): 250 mg/kg IV bolus in combination with sodium phenylacetate 250 mg/kg and sodium benzoate 250 mg/kg IV bolus over 90 to 120 minutes, followed by maintenance infusions of arginine 250 mg/kg/day in combination with sodium phenylacetate 250 to 500 mg/kg/day and sodium benzoate 250 to 500 mg/kg/day.

Maximum arginine dose 12 g/day, sodium phenylacetate 12 g/day and sodium benzoate 12 g/day [1]
Alternative dose (ASL Deficiency): 200 to 400 mg/kg IV bolus in combination with sodium phenylacetate 250 mg/kg and sodium benzoate 250 mg/kg IV bolus over 90 to 120 minutes, followed by maintenance infusions of arginine 200 to 400 mg/kg/day in combination with sodium phenylacetate 250 to 500 mg/kg/day and sodium benzoate 250 to 500 mg/kg/day. **Maximum arginine dose 12 g/day, sodium phenylacetate 12 g/day and sodium benzoate 12 g/day** [1]

Repeating the loading dose within 24 hours of the initial loading dose should be considered only for patients with a severe disorder receiving dialysis[5].

CPS = carbamyl phosphate synthetase; OTC = ornithine transcarbamylase; NAGS = N-acetyl glutamate synthase; ASS = argininosuccinic acid synthetase; ASL = argininosuccinic acid lyase

Uses

Adjunctive treatment of acute hyperammonemia in neonates with urea cycle disorders. Sodium phenylacetate/sodium benzoate should be used concomitantly with arginine hydrochloride. Hemodialysis is the primary treatment of acute hyperammonemia during the early management period [3][6][4][5][7].

Administration

For treatment of acute hyperammonemia, **must be administered through a central line.** For loading and maintenance doses, dilute arginine and sodium phenylacetate/sodium benzoate in 25 to 35 mL/kg of $D_{10}W$ prior to administration [5].

MEDICATION SAFETY

Contraindications/Precautions

Arginine hydrochloride contains 47.5 mEq of chloride in 100 mL. Hyperchloremic metabolic acidosis has been reported in 2 pediatric patients receiving excessive arginine. Extravasation can cause tissue necrosis. Arginine is a nitric oxide precursor. Excessive arginine accumulation can result in nitric oxide overproduction with potential for vasodilation and hypotension [6][4][5][8].

Solution Compatibility

$D_{10}W$ and sodium phenylacetate/sodium benzoate 10%.

Monitoring

Plasma ammonia levels every hour during dialysis until levels stabilize to less than 200 to 300 micromoles/L. Capillary blood should not be used for monitoring ammonia levels. Monitor electrolytes and acid-base status closely during the acute phase (eg, every 4 hours). Monitor amino acids daily to assess the effectiveness of citrulline/arginine replacement and glutamine removal [4][5].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

The use of arginine provides an alternative pathway for waste nitrogen excretion in patients with urea cycle disorders, attenuating the risk for ammonia- and glutamine-induced neurotoxicity. Arginine increases the synthesis of citrulline which contains a nitrogen from ammonia and is efficiently excreted in the urine. In addition, certain defects in the urea cycle prevent the formation of citrulline which decreases the synthesis of arginine. This results in arginine becoming an essential amino acid in patients with urea cycle disorders [6][4][7].

ABOUT

Special Considerations/Preparation

Arginine hydrochloride is supplied as a 10% solution. The product is hypertonic (950 mOsmol/liter), acidic (average pH 5.6), and contains 47.5 mEq of chloride in 100 mL. The product should be stored at room temperature. Solution that has been frozen should not be used [8].

Ascorbic Acid

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Adequate Intake:
40 mg/day orally or enterally [1].

Enteral Nutrition
Preterm: 18 to 24 mg/kg/day enterally [1].
Term:40 mg/day enterally [1].

Parenteral Nutrition
Preterm: 15 to 25 mg/kg/day IV. *Multivitamin formulations (80 mg/5 mL):* 5 mL for infants 3 kg or more; 3.25 mL for infants 1 to 3 kg, and 1.5 mL for infants less than 1 kg [1]
Term: 80 mg/day IV [1].

Uses

Pediatric FDA Approved Indications
Ascor® is indicated for the short-term (up to 1 week) treatment of scurvy in patients 5 months or older for whom oral administration is not possible, is insufficient, or is contraindicated [3].
Limitations of Use
Not indicated for the treatment of vitamin C deficiency not associated with signs and symptoms of scurvy [3].

Administration

Injection
•Dilute into a large volume such as normal saline or dextrose [2].
•Too rapid administration should be avoided [2].

MEDICATION SAFETY

Contraindications/Precautions

CONTRAINDICATIONS
None [2]

PRECAUTIONS
Administration: Avoid rapid administration [2]

Adverse Effects

Too rapid IV administration of the solution may cause temporary faintness or dizziness [2].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action
Ascorbic acid (vitamin C) is a water-soluble vitamin. Ascorbic acid is involved in tyrosine metabolism, conversion of folic acid to folinic acid, carbohydrate metabolism, synthesis of lipids and proteins, iron metabolism, resistance to infections, and cellular respiration [2].

Distribution
Ascorbic acid is widely distributed in the body. Large concentrations are found in the liver, leukocytes, platelets, glandular tissues, and eye lens [3].

Metabolism
The major route of metabolism involves conversion of ascorbic acid to urinary oxalate, presumably through intermediate formation of dehydroascorbic acid [3].

Excretion
Ascorbic acid is excreted by the kidney in large amounts only when plasma concentrations exceed 1.4 mg/100 mL [3].

Half-life: 7.4 +/- 1.4 hours [3]

ABOUT

Special Considerations/Preparation

Injection
Availability: Ascorbic acid 500 mg/mL [2]
Storage: Store under refrigerated conditions between 2 and 8 degrees C (36 and 46 degrees F). Protect from light [2]

Preparation:[2]
•Pressure may develop within vial during storage; relieve pressure by first inserting sterile empty syringe into vial to allow pressure to equilibrate.
•Once vial is punctured, complete all dispensing from the vial within 4 hours and use each dose immediately; discard unused portion .
•Dilute dose in compatible infusion solution.

Oral
Availability: Multiple forms and strengths, such as 100 mg, 250 mg, 500 mg, 1000 mg oral tablets; 500 mg chewable tablet; 500 mg and 1000 mg extended-release oral tablet; 60 mg mucous membrane lozenge/troche; 500 mg oral wafer.

Aspirin

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Acute Ischemic Stroke (AIS), Recurrent: 1 to 5 mg/kg orally once daily [1][2].

Thrombosis; Prophylaxis
1 to 5 mg/kg orally once daily [1][3][4][5].
Higher doses (6 to 10 mg/kg/day) have been used in neonates undergoing heart surgery [1][6][7][8].

Uses

Acute Ischemic Stroke (AIS): Secondary prevention of recurrent AIS [1][2][5].

Thrombosis; Prophylaxis: Aspirin is recommended as thromboprophylaxis after Fontan surgery, in patients with systemic-to-pulmonary shunts, in patients after ventricular assist device placement, and in patients with mechanical heart valves who have had thrombotic events while receiving therapeutic antithrombotic therapy or patients in whom there is a contraindication to full-dose vitamin K antagonists [1][3][4][5][9]. In a prospective, multicenter, randomized study (n=111) of warfarin vs aspirin for primary thromboprophylaxis in children after Fontan surgery, the thrombosis event rate at 2 years was 19% with no significant difference between warfarin and aspirin therapy (24% vs 14%; p=0.45); minor bleeding was more common in the warfarin group (33% vs 14%) [3].

Administration

Administer without regard to feedings.

MEDICATION SAFETY

Contraindications/Precautions

Aspirin use has been associated with a potentially fatal condition called Reye's syndrome. Association has been shown to be mainly dose dependent, occurring with anti-inflammatory doses (greater than 40 mg/kg/day), rather than lower doses used for antiplatelet effects

[11][12][5][13][14]. Use caution in patients with bleeding disorders, peptic ulcer disease, renal impairment, or severe hepatic impairment. Severe allergic reactions, including asthma, hives, and facial swelling, may occur [15].

Adverse Effects

Mild gastrointestinal symptoms (nausea, vomiting, abdominal pain, GI upset) are the most common adverse effects. Headache and tinnitus have also been reported frequently in children. Elevations in serum transaminases may occur [16][17]. Mild salicylism is characterized by headache, dizziness, tinnitus, hearing and vision impairment, sweating, nausea, vomiting, nasal congestion, and slight hyperpyrexia. Symptoms of severe salicylate toxicity include hyperventilation, mental confusion, restlessness, irritability, hyperthermia, and alterations in acid-base balance, primarily respiratory alkalosis [10].

Monitoring

Mild salicylism is characterized by headache, dizziness, tinnitus, hearing and vision impairment, sweating, nausea, vomiting, nasal congestion, and slight hyperpyrexia. Symptoms of severe salicylate toxicity include hyperventilation, mental confusion, restlessness, irritability, hyperthermia, and alterations in acid-base balance, primarily respiratory alkalosis [10].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action: The main mechanism of action of aspirin is through inhibition of prostaglandin biosynthesis. Prostaglandins are produced from arachidonic acid via COX (cyclooxygenase; also known as prostaglandin endoperoxide synthase). Aspirin is a more specific inhibitor against COX-1 over COX-2 [18]. Aspirin is a more potent inhibitor of both prostaglandin synthesis and platelet aggregation than its other salicylic derivatives due to the acetyl group on the aspirin molecule, which inactivates cyclooxygenase via acetylation [19]. The antithrombotic effect of aspirin occurs by an irreversible inhibition of platelet cyclooxygenase. This enzyme inhibition blocks the formation of thromboxane A2 from arachidonic acid which would reduce platelet shape change, aggregation, and the release reaction [20][21][22][23].

Platelet inhibition occurs at lower doses (1 to 5 mg/kg/day). Rapidly absorbed following oral administration with peak concentration achieved in 2 hours. Rapidly hydrolyzed by esterases in the liver, intestine, and blood to salicylic acid. Has a low Vd and is extensively bound to albumin (80% to 90%). Eliminated through hepatic metabolism and renal excretion with

elimination pathways dependent on dose. At therapeutic doses, most elimination occurs through hepatic metabolism to 3 major metabolites (all inactive); less than 10% is excreted unchanged in the urine. At higher doses, when saturation of metabolic pathways occurs, renal excretion dominates with greater than 50% of unchanged salicylic acid eliminated in the urine. Renal excretion dependent on urinary pH (alkaline urine increases elimination). Elimination half-life is approximately 2 to 3 hours at low dose and 12 hours at anti-inflammatory doses [18].

ABOUT

Special Considerations/Preparation

Availability: 81-mg chewable tablets; 300- and 600-mg rectal suppositories.
Storage, rectal suppositories: Store in a cool place between 8 and 15 degrees C (46 to 59 degrees F) or refrigerate.

Atropine

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Bradycardia
IV: 0.01 to 0.03 mg/kg/dose IV [1][2] over 1 minute, or IM. Dose can be repeated every 10 to 15 minutes to achieve desired effect, cumulative maximum dose of 0.04 mg/kg.
ET: 0.01 to 0.03 mg/kg/dose immediately followed by 1 mL NS.
Oral: Begin with 0.02 mg/kg/dose given every 4 to 6 hours. May increase gradually to 0.09 mg/kg/dose.

Premedication for Intubation
0.01 to 0.02 mg/kg IV over 1 minute immediately prior to other premedications [3][4][5][6][7].

Organophosphate Poisoning
Guideline: 0.02 mg/kg IV, doubled every 5 minutes; maintenance infusion, 10% to 20% of the total loading dose/hr, **MAX dosage 2 mg/hr (from adult dosing)**; titrate to reversal of bronchorrhea, bronchospasm, bradycardia, and hypotension [2]
Autoinjector (Atropen®)
Less than 7 kg, 2 or more mild symptoms and exposure is known or suspected: 0.25 mg IM (yellow label) into the mid-lateral thigh at first signs of poisoning; wait 10 to 15 minutes and if severe symptoms do not occur no further injections are necessary; if severe symptoms develop after treatment, administer an additional 2 injections (0.25 mg each; yellow label) in rapid succession [8]
Less than 7 kg, severe symptoms or unconscious: 3 IM injections of 0.25 mg each (yellow label) into the mid-lateral thigh in rapid succession at first signs of poisoning; if seizure is suspected in the unconscious patient, consider concurrent anticonvulsant, preferably a benzodiazepine [8]
Concomitant medications: A cholinesterase reactivator (eg, pralidoxime) may be given as adjunctive therapy [8]
• Closely supervise all patients for at least 48 to 72 hours following therapy [8]

Mild Symptoms	Severe Symptoms
Blurred vision, miosis	Strange or confused behavior
Excessive, unexplained teary eyes*	Severe difficulty breathing or copious secretions from lungs/airway
Excessive, unexplained runny nose*	Severe muscular twitching and general weakness**
Increased salivation such as sudden unexplained excessive drooling	Involuntary urination and defecation*

Chest tightness or difficulty breathing	Convulsions
Tremors throughout the body or muscular twitching	Unconsciousness
Nausea and/or vomiting	
Unexplained wheezing, coughing or increased airway secretions	
Acute onset of stomach cramps	
Tachycardia or bradycardia	
* These symptoms are sometimes observed in healthy infants and young children. In this age group, these symptoms are less reliable than other symptoms listed. Symptoms must be considered collectively when nerve agent or pesticide exposure is known or suspected.	
**Infants may become drowsy or unconscious, with muscle floppiness rather than muscle twitching soon after exposure to nerve agent or insecticides.	
Atropen® Product Information November, 2020	

Uses

Bradycardia

Guidelines: Severe bradycardia may occur due to poisoning with beta-blocker, calcium channel blocker, digoxin or local anesthetic agents. Treatment with atropine is recommended, and is a common first-line agent. Atropine has been used successfully to improve heart rate and blood pressure, although most supporting data are from case reports [2].
In addition to reversal of severe sinus bradycardia due to parasympathetic influences on the heart (digoxin, beta-blocker drugs, hyperactive carotid sinus reflex), atropine has also been administered in neonates to prevent bradycardia associated with agents used during endotracheal or nasotracheal intubation [3][4][5][6][7].

Organophosphate or Carbamate Poisoning

Guidelines: Organophosphates and carbamates, found in pesticides, nerve agents, and some medications, inhibit acetylcholinesterase and result in parasympathetic and nicotinic excess, and CNS effects. Atropine blocks parasympathetic overstimulation to mitigate bronchorrhea, bradycardia, bronchospasm, and CNS effects; it does not block acetylcholine excess at the neuromuscular junction or nicotinic ganglia and therefore does not reverse paralysis. Immediate administration of atropine is recommended for severe poisoning; early atropine administration improved survival in a clinical trial. Doses required are typically much

larger for this indication versus typical bradycardia. Dermal decontamination, early endotracheal intubation for life-threatening poisoning, and benzodiazepines for seizure control are also recommended [2].

Pediatric FDA Approved Indications
Atropine IM auto-injection is indicated for the treatment of poisoning by susceptible organophosphorus nerve agents having cholinesterase activity as well as organophosphorus or carbamate insecticides in adult and pediatric patients [8].

Administration

Intramuscular:
• Organophosphate poisoning: Autoinjectors (AIs) are recommended for IM delivery as opposed to IM administration with the needle and syringe method. AIs provide superior delivery by releasing the medication as the needle punctures the tissue compared with traditional IM delivery which creates a small pool of medication. AIs produce a quicker peak (less than 5 minutes) compared with the needle and syringe method (25 minutes), which is necessary for severe cholinergic crisis [9].
Atropen® Auto-injector 0.25 mg)
• Remove the gray safety release, bunch up the thigh to provide a thicker area for injection and inject at a 90-degree angle against the mid-lateral thigh; the device will activate and deliver medication [8].
• Hold the autoinjector firmly in place for at least 10 seconds to allow the injection to finish; remove the autoinjector and massage the injection site for several seconds [8].
• If the needle is not visible after injection, check to be sure the gray safety release has been removed, and repeat injection, but press harder [8].

Intravenous: Concentrations are 0.05-, 0.1-, 0.4-, and 1-mg/mL [10]. Administer IV over 1 minute [6] as undiluted drug (0.05- or 0.1-mg/mL).
Atropine may also be diluted in 4 mL of D_5 W or NS when used as a premedication [11].

Oral: May give IV dosage form orally.

MEDICATION SAFETY

Adverse Effects

Cardiovascular effects: Cardiac arrhythmias can occur, particularly during the first 2 minutes following IV administration; usually a simple A-V dissociation, more often caused by smaller rather than larger doses.

Gastrointestinal: Abdominal distention with decreased bowel activity, esophageal reflux.

Ophthalmic: Mydriasis and cycloplegia.

Other: Fever, especially in brain-damaged infants.

Respiratory: Post-operative respiratory acidosis was associated with pre-operative atropine 0.01 mg/kg IV compared with no atropine (22.9% vs 7.3%; p=0.016) in a retrospective analysis of 150 Asian neonates undergoing surgical ligation for patent ductus arteriosus. The mean capillary CO_2 was higher in the atropine compared with no atropine group (49.35 vs 38.85 mmHg; p=0.0004). The mean capillary pH was lower in the atropine compared with no atropine group (7.33 vs 7.43 mmHg; p=0.0001) [12].

Solution Compatibility

D_5W and NS.

Terminal Injection Site Compatibility

Amiodarone, cimetidine, dobutamine, famotidine, fentanyl, furosemide, glycopyrrolate, heparin, hydrocortisone succinate, meropenem, methadone, metoclopramide, midazolam, milrinone, morphine, nafcillin, netilmicin, pentobarbital, potassium chloride, propofol, ranitidine, and sodium bicarbonate.

Terminal Injection Site Incompatibility

Phenytoin, sulfamethoxazole/trimethoprim.

Monitoring

Toxic Physical Monitoring
Heart rate.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Anticholinergic. Increases heart rate by decreasing the effects of the parasympathetic system while increasing the effects of the sympathetic system. Peak tachycardia is 12 to 16 minutes

after dose is given. Relaxes bronchial smooth muscle, thus reducing airway resistance and increasing dead space by 30%. Motor activity in the stomach and small and large intestines is reduced. Esophageal sphincter tone is reduced. Salivary secretion is inhibited. Duration of action is 6 hours. Primarily excreted renally unchanged.

ABOUT

Special Considerations/Preparation

Injections
Supplied in multiple concentrations (0.05-, 0.1-,0.4-, and 1-mg/mL) for injection. May give IV dosage form orally.
IM, Autoinjector
Availability: 0.25 mg/0.3 mL, 0.5 mg/0.7 mL, 1 mg/0.7 mL, 2 mg/0.7 mL in prefilled single-dose autoinjectors [8]
Storage: Store auto-injector at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F). Do not freeze. Protect from light [8].

Azithromycin

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

KIDs List: Avoid use in neonates (unless treating Bordetella pertussis or Chlamydia trachomatis pneumonia; consider risk/benefit ratio when using for Ureaplasma) due to risk of hypertrophic pyloric stenosis [1].

Treatment and Prophylaxis of Pertussis Infections: 10 mg/kg/dose orally once daily for 5 days [2]; IV dose is unknown.

Ophthalmia neonatorum caused by *Chlamydia trachomatis:* 20 mg/kg/dose orally once daily for 3 days [3][4].

Ureaplasma Eradication
24 to 28 weeks gestational age: 20 mg/kg IV once daily for 3 days [5][6][7]

Uses

Bordetella; Treatment and Postexposure Prophylaxis: Azithromycin is the preferred agent for the treatment and postexposure prophylaxis of pertussis in infants younger than 1 month of age. Treat infants younger than 1 year within 6 weeks of cough onset. Prophylaxis should be administered within 21 days of onset of cough in the index patient [2].

Chlamydia Infections: Erythromycin base or ethylsuccinate is the first-line agent and azithromycin a second-line agent for the treatment of ophthalmia neonatorum caused by *Chlamydia trachomatis* ; however, data are limited on azithromycin [3].

Ureaplasma Eradication and Prevention of Bronchopulmonary Dysplasia (BPD)
Summary: Azithromycin 20 mg/kg IV for 3 days has been shown to be safe and effective for the eradication of *Ureaplasma* species in the respiratory tract of preterm neonates [5][6][7]; however, this has not translated into strong evidence that azithromycin treatment and *Ureaplasma* eradication have a preventative effect on the development of BPD. Some evidence points to the greatest benefit being in the subpopulation of neonates with lower respiratory tract colonization [10][5]
Eradication: Azithromycin at doses of 20 mg/kg IV for 3 days is effective for eradication of *Ureaplasma* colonization of the respiratory tract in preterm neonates [5][6][7], and has been found to be more effective than doses of 10 mg/kg/day [6]. Azithromycin was administered to neonates 24 to 28 weeks gestational age, with a postnatal age less than 72 hours, and positive pressure ventilation for at least 1 hour. All patients with positive *Ureaplasma* cultures became culture-negative after azithromycin treatment. No abnormal vital signs, arrhythmias, or episodes of feeding intolerance or infantile hypertrophic pyloric stenosis were reported in

the 3 studies (N=121[5]; N=15[6]; N=13[7]).
Prevention of BPD: Meta-analyses have reported conflicting evidence regarding the effect of azithromycin on the prevention of chronic lung disease in preterm neonates; however, the studies included in these meta-analyses have predominantly used azithromycin doses of 10 mg/kg/day for varying durations [11][12]. Other studies have found doses of 20 mg/kg/day to be more effective for *Ureaplasma* eradication [5][6][7]. Bronchopulmonary dysplasia at 36 weeks postmenstrual age (PMA) was reported in 45% treated with azithromycin 20 mg/kg IV for 3 days compared with 33% given placebo (N=121). Among the subgroup with *Ureaplasma* positive cultures (n=44), rates were 47% and 38%. Both are statistically nonsignificant results [5]. A 2-year follow up study reported that the composite endpoint of death or serious respiratory morbidity was not significantly different in those treated with azithromycin (34.8%) compared with placebo (30.4%); neurodevelopmental outcomes were also not significantly different between groups. A post-hoc analysis of those who were intubated and had a tracheal aspirate positive for *Ureaplasma* (lower respiratory tract colonization) found significantly higher rates of the composite endpoint of death or serious respiratory morbidity compared with those who were *Ureaplasma* negative, representing a subpopulation that may receive a greater benefit from azithromycin therapy; more studies are needed [10].

Administration

Intravenous: Dilute reconstituted solution (100 mg/mL) to a final concentration of 1 to 2 mg/mL. Give the 1 mg/mL concentration over 3 hours or 2 mg/mL concentration over 1 hour [8].
Oral: Oral suspension can be given with or without feeding [9].

MEDICATION SAFETY

Contraindications/Precautions

Contraindicated in patients allergic to macrolide or ketolide antibiotics and patients with a history of cholestatic jaundice/hepatic dysfunction associated with prior use of azithromycin [13].

Precautions
Cardiovascular: QT-interval prolongation has been reported including cases of torsade de pointes. Patients with known or congenital QT prolongation, history of torsade de pointes, bradyarrhythmias, uncompensated heart failure, ongoing proarrhythmic conditions (eg, significant bradycardia, uncorrected hypokalemia or hypomagnesemia, or those receiving class IA or class III antiarrhythmic agents), or concomitant drugs known to prolong the QT interval are at increased risk [14][15][16].
Cardiovascular: A possible increased risk of acute cardiovascular death has been observed. Risk was noted to be greater during the first 5 days of therapy. Consider balancing risk with treatment benefits [17].

Cardiovascular: Compared with penicillin or a cephalosporin, azithromycin was not associated with greater prevalence of cardiac arrest, overall mortality, or ventricular arrhythmias in a retrospective cohort study of 82,982 pediatric patients (median age 2.6 years) with community acquired pneumonia [18].

Gastrointestinal: Infantile hypertrophic pyloric stenosis has been reported in neonates up to 42 days of life treated with azithromycin [19].
Gastrointestinal: Clostridioides difficile associated diarrhea (CDAD) has been reported; may range in severity from mild diarrhea to fatal colitis. If CDAD is confirmed, discontinue therapy and initiate appropriate fluid/electrolyte management, protein supplementation, antibacterial drug treatment for C difficile, and surgical evaluation if clinically indicated [17].
Hepatic: Hepatotoxicity (eg, abnormal liver function, hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure), including fatalities, has been reported; if signs and symptoms of hepatitis occur, discontinue therapy [13].
Immunologic: Serious and sometimes fatal allergic reactions, including angioedema, anaphylaxis, and dermatologic reactions such as acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported. Immediate discontinuation recommended; however, recurrence of allergic symptoms without further azithromycin exposure may occur [20][21].
Long-term use: Avoid long-term azithromycin use for prophylaxis of bronchiolitis obliterans syndrome (unapproved use) to patients who undergo donor stem cell transplants due to the increased potential for cancer relapse and death [22].
Neurologic: Worsening of myasthenia gravis symptoms as well as new onset of myasthenia gravis has been reported rarely in association with azithromycin [13][23].

Adverse Effects

Diarrhea and/or vomiting occur in 5% to 12% of patients. Irritability, rash, and blood in stool have also been reported.
The most frequently reported gastrointestinal symptoms were vomiting, diarrhea, abdominal tenderness, and feeding intolerance in a systematic review of 11 articles (n=473 neonates) [24]
The use of macrolide antibiotics was associated with infantile hypertrophic pyloric stenosis with a 30-fold increased risk in infants exposed at 0 to 13 days of age and 3-fold increased risk in infants exposed at 14 to 120 days of age in an observational study (n=6591) [25].
Similar outcomes (highest risk of pyloric stenosis when exposed within the first couple weeks of life; although risk still present at 6 weeks of life) were demonstrated in another observational study (n= 4875 exposed to azithromycin) [26].

Solution Compatibility

D_5W, NS, 5% Dextrose in 0.45% NaCl with 20 mEq/L KCl, and Lactated Ringer's.

Terminal Injection Site Compatibility

Caspofungin.

Terminal Injection Site Incompatibility

Amikacin, aztreonam, cefotaxime, ceftazidime, ceftriaxone, cefuroxime, clindamycin, famotidine, fentanyl, furosemide, gentamicin, imipenem-cilastatin, morphine, piperacillin-tazobactam, potassium chloride, ticarcillin-clavulanate, and tobramycin.

Monitoring

Assess gastrointestinal tolerance.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Azithromycin is classified as an azalide, a subclass of macrolide antibiotics. In vitro activity has been demonstrated against *Bordetella pertussis*, as well as Streptococci (Groups C, F, G and Viridans), *Ureaplasma urealyticum*, and Peptostreptococcus species. Eradication of *B. pertussis* in unimmunized individuals (e.g., neonates) takes longer and requires higher doses than immunized individuals. Oral bioavailability is 38% in adults and children and is not affected by food. Primarily excreted unchanged in the bile, with some hepatic metabolism to inactive metabolites. The prolonged terminal half-life (approximately 80 hours) is thought to be due to extensive uptake and subsequent release of drug from tissues.

ABOUT

Special Considerations/Preparation

Oral
Availability: Oral suspension is available in 300, 600, 900, and 1,200 mg bottles.
Reconstitute 300 mg bottle with 9 mL of water to provide a final concentration of 100 mg per 5 mL (20 mg/mL). Shake well before administration.

Storage: Do not refrigerate. Use within 10 days once bottle has been opened.

Injection
Availability: Azithromycin for intravenous injection is supplied in single use vials containing 500 mg lyophilized powder. *Reconstitute* by adding 4.8 mL Sterile Water for Injection, then shake the vial until all the drug is dissolved. The concentration of the reconstituted solution is 100 mg/mL.
Storage: It is stable at room temperature for 24 hours.
Dilute prior to administration using a compatible solution to a final concentration of 1 to 2 mg/mL. Diluted solution stable for 24 hours at room temperature or 7 days in refrigerator. Do not use higher concentrations due to local IV site reactions. **Infuse over at least 60 minutes.**

Aztreonam

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

30 mg/kg/dose IV or IM.

Antibiotic Dosing Chart:
Renal function and drug elimination are most strongly correlated with Postmenstrual Age (PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.

Dosing Interval Chart		
PMA (weeks)	**PostNatal (days)**	**Interval (hours)**
≤29	0 to 28 >28	12 8
30 to 36	0 to 14 >14	12 8
37 to 44	0 to 7 >7	12 8
≥45	ALL	6

Uses

Treatment of neonatal sepsis caused by susceptible gram-negative organisms (e.g. *E coli*, *H influenzae*, *Klebsiella, Pseudomonas,* and *Serratia*). Generally used in combination with ampicillin (empirical treatment of sepsis) or an aminoglycoside (for synergism against *Pseudomonas* and *Enterobacteriaceae*).

Administration

Intravenous
Give IV push over 3 to 5 minutes, or IV infusion over 20 to 60 minutes at a final concentration **not to exceed 20 mg/mL**[1][2].
Intramuscular
For IM administration, concentrations range from 66 mg/mL to 333 mg/mL [1].

MEDICATION SAFETY

Adverse Effects

Aztreonam contains 780 mg L-arginine per gram of drug (23.4 mg/kg body weight per dose). Adequate amounts of glucose must be provided to prevent hypoglycemia. Side effects are rare but include eosinophilia, elevation of serum transaminases, and phlebitis at the injection site.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Amikacin, aminophylline, ampicillin, bumetanide, calcium gluconate, caspofungin, cefazolin, cefepime, cefotaxime, cefoxitin, ceftazidime, ceftriaxone, cimetidine, clindamycin, dexamethasone, dobutamine, dopamine, enalaprilat, famotidine, fluconazole, furosemide, gentamicin, heparin, hydrocortisone succinate, imipenem, insulin, linezolid, magnesium sulfate, metoclopramide, mezlocillin, morphine, netilmicin, nicardipine, piperacillin, piperacillin/tazobactam, potassium chloride, propofol, quinupristin/dalfopristin, ranitidine, remifentanil, sodium bicarbonate, ticarcillin/clavulanate, tobramycin, vancomycin, and zidovudine.

Terminal Injection Site Incompatibility

Acyclovir, amphotericin B, azithromycin, ganciclovir, lorazepam, metronidazole, and nafcillin.

Monitoring

Check serum glucose one hour after administration. Measuring serum concentration is not usually necessary. Periodic CBC, AST, ALT.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action: Aztreonam is a synthetically-produced monocyclic beta-lactam antibiotic. Although bactericidal against aerobic gram-negative bacteria, it has virtually no activity against aerobic gram-positive and anaerobic bacteria, thereby producing little alteration of bowel flora [1].

Good tissue and fluid penetration has been demonstrated in adults, along with protein-binding of 50 to 65%. Eliminated renally, primarily as unchanged drug. Serum half-life in neonates is 3 to 9 hours. Aztreonam does not interfere with bilirubin-albumin binding.

ABOUT

Special Considerations/Preparation

Availability: Powder for injection in 1-g and 2-g vials [3]
Reconstitution (Shake immediately and vigorously):

- For infusion, reconstitute 1-g with at least 3 mL of sterile water for injection (SWFI) and further dilute to a concentration of no greater than 20 mg/mL.
- For bolus, reconstitute 1-g or 2-g vial with 6 to 10 mL of SWFI.
- For IM administration, dilute 1-g with at least 3 mL of appropriate diluent.

Storage: Prior to reconstitution, store in original package at a controlled room temperature; avoid excessive heat [3].
Solutions at concentrations not exceeding 2% weight/volume must be used within 48 hours if stored at a controlled room temperature between 15 and 30 degrees C (59 and 86 degrees F) or within 7 days if refrigerated between 2 and 8 degrees C (36 and 46 degrees). Discard any unused portion. [3].
Solutions at concentrations exceeding 2% weight/volume, except those prepared with Sterile Water for Injection or Sodium Chloride Injection, should be used promptly after preparation; the 2 excepted solutions must be used within 48 hours if stored at a controlled room temperature between 15 and 30 degrees C (59 and 86 degrees F) or within 7 days if refrigerated between 2 and 8 degrees C (36 and 46 degrees). Discard any unused portion [3].

DOSING/ADMINISTRATION

Dose

Respiratory Distress Syndrome (RDS)
4 mL/kg/dose (100 mg of phospholipids/kg/dose) intratracheally in 4 quarter-dose aliquots with the infant in a different position for each aliquot [1]
Prophylaxis: First dose is given as soon as possible, preferably within 15 minutes of birth, up to 4 doses may be administered in first 48 hours of life, if indicated. Do not give more frequently than every 6 hours. Obtain radiographic confirmation of respiratory distress syndrome before administering additional doses[1].
Rescue treatment of RDS : First dose is as soon as possible, preferably by 8 hours of age; up to 4 doses may be administered in first 48 hours of life, if indicated. Do not give more frequently than every 6 hours [1]

Uses

Prevention and treatment of respiratory distress syndrome (RDS) in premature infants. Routine continuous positive airway pressure (CPAP) is considered superior to prophylactic surfactant therapy. It is strongly recommended that CPAP immediately after birth with subsequent selective surfactant administration be considered as an alternative to routine intubation with prophylactic or early surfactant administration in preterm infants. Severe RDS in preterm infants born younger than 30 weeks gestation who need mechanical ventilation should be administered surfactant after initial stabilization. Consider the use of rescue surfactant for infants with hypoxic respiratory failure attributable to secondary surfactant deficiency, such as meconium aspiration syndrome or sepsis/pneumonia[2].
Animal-derived surfactants (beractant, calfactant, and poractant alfa) had comparable outcomes for air leak syndromes, death, and bronchopulmonary dysplasia in a retrospective study (n=51,282; median birth weight of 1435 g; median gestational age of 30 weeks (27 to 33 weeks)) [3]. In a prospective randomized trial, the animal-derived surfactants all improved FiO2 need, PaO2 values, chest x-ray findings, and lung ultrasonography (LUS) scores (N=62, gestational age range 24 to 34 weeks, birthweight range 560 to 2500 g). However, the results were significantly better with poractant alfa and beractant compared with calfactant. The FiO2 values at 24 hours post-surfactant for poractant alfa, beractant, and calfactant were 36.8%, 33.6%, and 53.1%, respectively. The PaO2 values at 24 hours post-surfactant for poractant alfa, beractant, and calfactant were 64.7, 66.3, and 61.3 mmHg, respectively. The LUS scores at 24 hours post-surfactant for poractant alfa, beractant, and calfactant were 3.8, 4.3, and 6.9, respectively. Significantly more calfactant-treated patients required repeat dosing. Mechanical ventilation duration and hospital length of stay were similar between all 3 groups [4].

Neonatal FDA-Approved Indications: Indicated for prevention and treatment ("rescue")

of Respiratory Distress Syndrome (RDS) (hyaline membrane disease) in premature infants. Beractant significantly reduces the incidence of RDS, mortality due to RDS, and air leak complications [1].

Administration

• For intratracheal use only [1]
• Administration is facilitated if one person administers the dose while another person positions and monitors the infant [1].
• At discretion of the clinician, the endotracheal tube may be suctioned prior to administration of beractant; allow infant to stabilize before proceeding with dosing [1].
• Slowly withdraw the contents of the vial into a plastic syringe through a large gauge needle (eg, at least 20 gauge). Attach the premeasured 5 French end-hole catheter to the syringe and fill the catheter with beractant, discarding any excess product through the catheter so that only the total dose to be given remains in the syringe [1].
• Administer in 4 quarter-dose aliquots with the infant in a different position for each aliquot as follows: 1) head and body inclined 5 to 10 degrees down, head turned to right; 2) head and body inclined 5 to 10 degrees down, head turned to left; 3) head and body inclined 5 to 10 degrees up, head turned to right; 4) head and body inclined 5 to 10 degrees up, head turned to left [1]
• For each quarter-dose aliquot, insert the 5-French end-hole catheter into the endotracheal tube with the tip of the catheter protruding just beyond the end of the endotracheal tube above the infant's carina; do not instill product into a mainstem bronchus. Gently inject the aliquot through the catheter over 2 to 3 seconds then remove the catheter and manually ventilate the infant for at least 30 seconds or until clinically stable. Use sufficient oxygen to prevent cyanosis and sufficient positive pressure to provide adequate air exchange and chest wall excursion [1].
• When the infant is stable following administration of an aliquot, reposition for instillation of the next quarter dose and then instill the dose using the same procedures [1].
• Once the final quarter-dose is administered, remove the catheter without flushing it. Do not suction the infant for 1 hour after dosing unless signs of significant airway obstruction occur [1].
• Each vial is for single-use only; discard unused product [1]

MEDICATION SAFETY

Contraindications/Precautions

Contraindications
No specific contraindications have been determined [1]

Precautions
Cardiovascular: Transient bradycardia and decreased oxygen saturation have been reported. Interrupt therapy and institute treatment as necessary [1]

Respiratory: Rapid effects on oxygenation and lung compliance occur with administration; intubation and ventilator management must be immediately available and frequent monitoring is required [1]
Immunologic: Post-treatment nosocomial sepsis may occur [1]
Respiratory: Rales and moist breath sounds have been reported after administration; endotracheal suctioning is not necessary unless airway obstruction present [1]

Adverse Effects

Most common reactions reported include transient bradycardia (11.9% of doses) and oxygen desaturation (9.8% of doses). Other adverse events include hypotension, endotracheal tube reflux or blockage, hypertension, hypercarbia, hypocarbia, vasoconstriction, pallor, and apnea. In a pooled analysis of all controlled studies, the incidence of intracranial hemorrhage (ICH) was not different between the Survanta® group and the control group; however, in 2 of the studies (single-dose rescue study and multiple-dose prevention study), the incidence of ICH was significantly higher in patients who received Survanta® compared with those in the control group (63.3% vs 30.8%; p=0.001 and 48.8% vs 34.2%; p=0.047, respectively) [5].

Monitoring

Monitor systemic oxygen and carbon dioxide levels with arterial or transcutaneous measurements frequently during therapy [5].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Survanta® is a modified natural bovine lung extract containing phospholipids, neutral lipids, fatty acids, and surfactant-associated proteins B and C, to which colfosceril palmitate (dipalmitoylphosphatidylcholine (DPPC)), palmitic acid, and tripalmitin are added. Resulting drug provides 25 mg/mL phospholipids (including 11 to 15.5 mg/mL disaturated phosphatidylcholine), 0.5 to 1.75 mg/mL triglycerides, 1.4 to 3.5 mg/mL fatty acids, and less than 1 mg/mL protein. Survanta® is suspended in NS and heat sterilized. Animal metabolism studies show that most of a dose becomes lung-associated within hours of administration, and lipids enter endogenous surfactant pathways of reuse and recycling [5].

ABOUT

Special Considerations/Preparation

Availability: 4- and 8-mL single-use vials (25 mg phospholipids/mL) [5]
Storage: Refrigerate at 2 to 8 degrees C (36 to 46 degrees F) and protect from light. Inspect Survanta® for discoloration; normal color is off-white to light-brown. If settling occurs during storage, **swirl** vial gently. **Do not shake.** Vials should be entered only once. Used vials with residual drug should be discarded. Unopened vials that have been warmed to room temperature one time may be refrigerated within 24 hours and stored for future use. Should not be warmed and returned to the refrigerator more than once [5].

Preparation
•If a prevention dose is to be given, begin preparation of product prior to infant's birth [1]
•After removing unopened vial from the refrigerator, warm at room temperature for at least 20 minutes or warm in hand for at least 8 minutes, do not warm by artificial warming methods [6]
•Do not shake vial; swirl gently to redisperse. Some foaming at the surface may occur during handling and is inherent in the nature of the product [6].
•Do not filter product [6]
•After warming vial, unopened vials can be returned to refrigerator within 24 hours of warming to store only once, record date and time when vial is removed from the refrigerator. Vials may not be out of refrigerator for more than 24 hours [6].
•Does not require reconstitution or sonication before use [6]

DOSING/ADMINISTRATION

Dose

Long-term benefits and safety and optimal regimens are unknown[1].

Retinopathy of prematurity, Type 1

Most common dose used in studies was 0.625 mg in 0.025 mL per eye via intravitreal injection for 1 dose [2][3].

Uncontrolled trials evaluated lower doses [4][5][6]; 0.312 mg in 0.025 mL [5] and 0.16 mg in 0.025 mL [4].

A phase 1 dose de-escalation study, demonstrated improvement by 5 days and no recurrence requiring additional treatment within 4 weeks for bevacizumab doses of 0.25 mg in 11 of 11 eyes, 0.125 mg for 14 of 14 eyes, 0.063 mg for 21 of 24 eyes, and 0.031 mg for 9 of 9 eyes of infants with severe ROP, type 1 [6].

Combination bevacizumab 0.25 mg in 0.01 mL with zone 1 sparing laser or deferred laser treatment was used [7].

Retreatment may be needed after 55 weeks' postmenstrual age [8]. Some infants required retreatment at a mean of 9.8 weeks (6 to 15 weeks) after the initial injection [4]

Premedication/Post-procedure medication

In infants, eyes were prepared with a topical anesthesia (0.5% proparacaine or 0.5% tetracaine) and ophthalmic antiseptic (5% [9][3][2] or 10% [10] povidone iodine) . After the procedure ophthalmic antibiotic drops were administered for 7 days [2].

Uses

Retinopathy of Prematurity (ROP)

A systematic review (5 randomized or semi-randomized studies) demonstrated no reduction in retinal detachment or recurrent ROP in infants treated with intravitreal bevacizumab (n=4 studies) or ranibizumab (n=1 studies) compared with laser therapy; however, refractive errors were reduced. In a subgroup analysis, the risk of recurrence was lower in type 1, but higher in type 2 ROP. Intravitreal bevacizumab was well tolerated but long-term systemic effects are unknown [1]. If bevacizumab is offered, consider only for type 1 ROP treatment in patients with zone I or posterior zone II disease [8].

In infants with stage 3+ ROP in each eye, intravitreal 0.625 mg bevacizumab significantly reduced the rate of recurrence compared with conventional laser therapy (6% vs 26%; P=0.002) at 54 weeks' postmenstrual age in a randomized trial (N=143 infants). However, a significant treatment effect was observed for zone I but not zone II posterior ROP. (Bevacizumab Eliminates the Angiogenic Threat of ROP (BEAT-ROP) Trial) [2]. At 2.5 years of age (n=109), a follow-up of the BEAT-ROP trial detected more myopia and very high myopia in laser-treated eyes compared with bevacizumab-treated eyes [11].

In a retrospective study of 241 infants, the ROP recurrence rate was 8.3% with bevacizumab. The recurrence rate was higher in those infants with APROP (31.6%) compared with infants

with stage 3+ ROP (6.3%; P less than 0.001) [12]. A follow-up (n=39 eyes) with fluorescein angiograph in infants at 4 years of age detected significant ocular-vascular abnormalities in bevacizumab (0.5 mg)-treated eyes compared with laser-treated eyes treated for type 1, zone I ROP [13]

For 2 months after intravitreal bevacizumab (0.625 mg/dose per eye or 0.25 mg/dose per eye), serum vascular endothelial growth factor (VEGF) and insulin-like growth factor-1 concentrations had greater suppression compared with laser surgery in 24 infants. Serum vascular endothelial growth factor concentrations for intravitreal bevacizumab groups (0.5 mg and 1.25 mg) were 50% lower from day 2 to day 60 compared with laser-treated groups (no bevacizumab). There were no significant differences in serum VGEF concentrations between the 2 bevacizumab doses. The clinical significance of these findings is unknown [14].

Pediatric FDA Approved Indications
Safety and effectiveness have not been established in pediatric patients [15].

Administration

Intravitreal Administration
• Bevacizumab concentration was 25 mg/mL [2][3]. Diluted concentrations, 3.1 mg/mL to 12.5 mg/mL, have been used with smaller doses [4][5][6].
•In pediatric patients a sterile 30-gauge [4][9], 31-gauge [3], or 32-gauge [10] 4-mm needle injected intravitreally 0.75 mm [10] to 1 mm [4][10][3] or 1.5 mm [9] to 2 mm [4] posterior to the temporal limbus into the vitreous cavity [10].

MEDICATION SAFETY

Contraindications/Precautions

Contraindications
Specific contraindications have not been determined [18]

Precautions
IV Administration
Cardiovascular: Increased risk for severe (Grade 3 or 4) hypertension; interruption or discontinuation may be necessary [18]
Cardiovascular: Congestive heart failure (CHF) and decline in LVEF have been reported; discontinuation may be necessary [18]
Concomitant use: Not indicated for use with anthracycline-based chemotherapy [18]
Dermatologic: Necrotizing fasciitis, including fatal cases, has been reported; usually secondary to wound healing complications, gastrointestinal perforation, or fistula formation; discontinuation may be necessary [18].
Fistulae: Non-gastrointestinal fistulae (ie, tracheoesophageal, bronchopleural, biliary, vaginal, renal, bladder), which may be serious and/or fatal, have been reported;

discontinuation may be required [18]
Gastrointestinal: Gastrointestinal: Serious gastrointestinal fistulae, including gastrointestinal-vaginal fistula, have been reported and may be accompanied by bowel obstruction requiring surgical interventions; discontinuation may be necessary [18]
Gastrointestinal: Serious and sometimes fatal gastrointestinal perforation has been reported, with highest incidence within 50 days of the first dose and in patients with a history of prior pelvic radiation; perforation may be complicated by intra-abdominal abscess, fistula formation, and need for diverting ostomies; discontinuation may be necessary [18]
Gastrointestinal: Avoid use in patients with ovarian cancer who have evidence of recto-sigmoid involvement by pelvic examination or bowel involvement on CT scan or clinical symptoms of bowel obstruction [18]
Hematologic: Thrombotic microangiopathy has been reported; monitoring recommended and discontinuation may be needed [18]
Hematologic: Serious and sometimes fatal arterial thrombotic events (ie, cerebral infarction, angina, transient ischemic attack, myocardial infarction) have been reported, with an increased risk in patients with a history of arterial thromboembolism or diabetes. The highest incidence was reported in patients with glioblastoma. Discontinue use if severe event is suspected [18]
Hematologic: Severe or fatal hemorrhage, including hemoptysis, gastrointestinal bleeding, hematemesis, CNS hemorrhage, epistaxis, and vaginal bleed, and minor hemorrhage have been reported; screening may be required and discontinuation may be necessary. Do not administer in patients with recent history of hemoptysis of 0.5 teaspoon or more of red blood [18].
Hematologic: Venous thromboembolic events have been reported; discontinuation may be required [18]
Immunologic: Infusion reactions (ie, hypertension, hypertensive crisis with neurological signs and symptoms, wheezing, oxygen desaturation, hypersensitivity and anaphylactoid/anaphylactic reactions (Grade 3), chest pain, headache, rigors, and diaphoresis) have been reported; if severe reaction occurs, stop infusion and institute appropriate therapy [18]
Neurologic: Posterior reversible encephalopathy syndrome (PRES) has been reported, occurring from 16 hours up to 1 year after treatment initiation. MRI is required to confirm diagnosis. Discontinue use in patients developing PRES [18]
Renal: Nephrotic syndrome, sometimes fatal, has been reported; discontinue use [18]
Renal: Proteinuria has been reported; interruption of therapy may be necessary [18]
Reproductive: Ovarian failure has been reported [18]
Respiratory: Serious and/or fatal pulmonary hemorrhage has been reported; discontinue use if suspected. Do not administer in patients with recent history of hemoptysis of 0.5 teaspoon or more of red blood [18]
Surgery and wound healing: The incidence of wound healing and surgical complications was increased in patients receiving bevacizumab; discontinuation may be necessary. Withhold bevacizumab for at least 28 days prior to elective surgery and do not administer bevacizumab for at least 28 days following major surgery until adequate wound healing [18].

Adverse Effects

Cardiovascular: Hypotension was reported in a male preterm infant twin 1 day after

intravitreal bevacizumab for retinopathy of prematurity. At 9 weeks, intravitreal injection of bevacizumab 0.625 mg/0.025 mL was administered in each eye under IV ketamine (0.3 mg) and local atropine (0.25%). Feeding intolerance, hypotension (42/24 mmHg), and oxygen desaturation (arterial oxygen saturation, 80%) were observed 22 hours after bevacizumab administration and continued the following day. Shortness of breath with apnea and lethargy were also noted. Intubation for mechanical ventilation, treatment with DOPamine, and prophylactic antibiotics were instituted. Blood pressure normalized on day 3 and his general condition improved. On day 6, DOPamine and antibiotics were discontinued. He was successfully extubated on day 7 and arterial oxygen saturation was normal. The sibling received bevacizumab with no episodes of hypotension [19]

Musculoskeletal: Non-mandibular osteonecrosis has been reported in patients younger than 18 years who received IV bevacizumab [15].

Neurologic: In a retrospective study (n=125), the adjusted odds ratio was 3.1 (95% CI, 1.2 to 8.4) for severe neurodevelopmental disability in intravitreal bevacizumab-treated compared with laser-treated preterm infants at 18 months corrected age after adjusting for gestational age, gender, maternal education, Score for Neonatal Acute Physiology-II score, bronchopulmonary dysplasia, sepsis, and severe brain injury [20].

Ophthalmic: More high myopia was seen in eyes treated with bevacizumab (14.6%) than those treated with ranibizumab (0%; p=0.03) at 1 year of age in a retrospective study (n=37 infants) [21].

Black Box Warning

IV Administration
Gastrointestinal Perforations: The incidence of gastrointestinal perforation, some fatal, in patients receiving bevacizumab ranged from 0.3 to 3%. Discontinue bevacizumab in patients who develop gastrointestinal perforation.
Surgery and Wound Healing Complications: The incidence of wound healing and surgical complications, including serious and fatal complications, is increased in patients receiving bevacizumab. Discontinue bevacizumab in patients who develop wound healing complications that require medical intervention. Withhold bevacizumab at least 28 days prior to elective surgery. Do not administer bevacizumab for at least 28 days after surgery and until the wound is fully healed.
Hemorrhages: Severe or fatal hemorrhage, including hemoptysis, gastrointestinal bleeding, hematemesis, central nervous systems (CNS) hemorrhage, epistaxis, and vaginal bleeding occur up to 5-fold more frequently in patients receiving bevacizumab. Do not administer bevacizumab to patients with a recent history of hemoptysis. Discontinue in patients who develop Grade 3 to 4 hemorrhage [15]

Solution Compatibility

NS

Solution Incompatibility

D^5W

Monitoring

The duration for follow-up is unknown but will require longer follow-up compared with laser treatment [12][8] due to delayed or incomplete vascularization, significant rates of recurrence and need for retreatment, and potential for developmentally abnormal or atypical retinal vascular features [8].
In a retrospective case series recurrent ROP occurred a mean of 51.2 weeks (range, 45.7 to 64.9 weeks) adjusted age after intravitreal bevacizumab in 20 infants [12]. Additionally retinal detachment had occurred in 2 treated patients at the age of 2.5 years [16] and 3 years [17].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action
Bevacizumab, a recombinant humanized monoclonal immunoglobulin-1 antibody, binds to vascular endothelial growth factor (VEGF) and inhibits the interaction of VEGF to Flt1 and KDR receptors on the surface of endothelial cells. In the process, it prevents the proliferation of endothelial cells and formation of new blood vessels [15].

Pharmacokinetics
Intravitreal Administration in infants
Serum concentrations
0.5 mg (0.25 mg/dose per eye): 0 on day 0, 72.9 ng/mL on day 2, 424 ng/mL on day 14, 172.5 ng/mL on day 42, and 78.7 ng/mL on day 60 [14]
1.25 mg (0.625 mg/dose per eye): 0 on day 0, 203.4 ng/mL on day 2, 1002 ng/mL on day 14, 444.4 ng/mL on day 42, and 305.6 ng/mL on day 60 [14]
Half-life: 21 days in 17 infants after intravitreal administration [14].

IV Administration in adults
Clearance: 0.23 L/day [15].
Distribution: 2.9 L [15].
Half-life: 20 days (range, 11 to 50 days) [15]

ABOUT

Special Considerations/Preparation

Availability: 100 mg/4 mL (25 mg/mL) and 400 mg/16 mL (25 mg/mL) sterile solution for IV infusion [15]
Storage: Store in the original carton and under refrigerated conditions between 2 and 8 degrees C (36 and 46 degrees F). Protect from light. Do not freeze or shake. Diluted solution may be stored between 2 and 8 degrees C (36 and 46 degrees) for up to 8 hours if not used immediately [18].

Stability (Bevacizumab for intravitreal injection is not commercially available and bevacizumab IV solution is frequently repackaged for this use.)
• Over a 6 month period, the stability of bevacizumab 25 mg/mL IV solution in polycarbonate and polypropylene syringes (0.13 mL/syringe) was compared with bevacizumab in glass vials during storage at a constant temperature of 2 to 8 degrees C. There was no significant difference in the quality of vascular endothelial growth factor (VEGF) binding and protein physical stability of bevacizumab in the syringes compared with the glass vials [22].
•The stability of bevacizumab 25 mg/mL IV solution repackaged as **1.25 mg/0.05 mL and 2.5 mg/0.1 mL** using 1 mL plastic, latex-free, tuberculin syringes was evaluated when stored under refrigeration at 4 degrees C for 1 week, 3 weeks, 3 months, and 6 months, and when frozen at -10 degrees C. Stability was evaluated based on binding activity to vascular endothelial growth factor (VEGF-165). The refrigerated syringes lost approximately 1.6% and 0% binding activity at 1 and 3 weeks, and lost 8.8% and 15.9% binding activity at 3 and 6 months. The frozen syringes lost 12% binding activity at 6 months. Pierced vials lost 9.6% and 12.7% binding activity at 3 and 6 months when stored under refrigeration [23].

Bumetanide

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

0.005 to 0.05 mg/kg/dose IV slow push, IM, or orally. Doses up to 0.1 mg/kg have been used in neonates; however, there are no pharmacodynamic data showing doses greater than 0.05 mg/kg provide additional benefit [1][2][3].
Preterm infants less than 34 weeks gestation in the first 2 months of life: every 24 hours.
Afterward: every 12 hours.

Preterm infants 34 weeks or more gestation and term infants in the first month of life: every 24 hours.
Afterward: every 12 hours.

Infants with lung disease and normal renal function should be started on a low dose. Infants with congestive heart failure or abnormal renal function will need a higher dose.

In a dose-range evaluation of bumetanide pharmacodynamics in critically ill neonates and infants, single IV doses ranging from 0.005 to 0.1 mg/kg (increases in increments of 0.005 mg/kg) were given over 1 to 2 minutes. All doses were associated with at least a 2-fold increase in urine output and electrolyte excretion rates. The dose range corresponding to the maximal effect was 0.035 to 0.04 mg/kg. There were no pharmacodynamic advantages (urine output and electrolyte excretion rate) to doses greater than 0.05 mg/kg [1]. Although doses of 0.05 and 0.1 mg/kg have been studied in neonates, only pharmacokinetic endpoints were determined, and no pharmacodynamic endpoints were reported [2]. In a retrospective study in preterm infants with oliguric renal failure and inadequate response to furosemide, bumetanide was effective in significantly increasing urine output in 29 of 35 infants. The mean bumetanide dose and duration of therapy were 0.03 +/- 0.016 mg/kg every 12 to 24 hours and 5.9 days, respectively. Urine output increased from 0.6 +/- 0.6 mL/kg/hour to 3 +/- 2.1 mL/kg/hour [3].

Diuresis, in Critically-Ill Patients: 1 to 10 mcg/kg/hr continuous IV infusion; mean study dose, 5.7 mcg/kg/hr; median duration, 3.3 days [4].

Uses

Diuresis, in Critically-Ill Patients: Preliminary evidence shows that the use of bumetanide as a continuous infusion in critically-ill pediatric patients (7 neonates and 33 children) improves urine output and helps patient achieve negative fluid balance. Urine output increased from 2.5 mL/kg/hr before bumetanide continuous infusion to 4.4 mL/kg/hr at the midpoint of the 30 mcg/kg/hr bumetanide infusion [6]. In a second study, negative

fluid balance was achieved by 54% of patients within 12 hours and 76% of patients by 48 hours when given a mean dose of 5.7 mcg/kg/hr bumetanide continuous infusion (N=95). Median age was 0.2 years (range, 0 to 15.7 years) [4]. The median duration of therapy ranged from 3.3 to 4.1 days [6][4]. One study reported potassium less than 3 mEq/L in 33% and SCr 1.5x or greater above baseline in 5% [4].
Heart Failure or Edema: Diuretic used in patients with renal insufficiency, congestive heart failure, or significant edema that is refractory to furosemide.
In neonates with pulmonary hypertension, supportive care with diuretics may be used cautiously for signs of right-sided heart failure [7].

Administration

Intravenous: Give undiluted over 1 to 2 minutes [1].
Oral: The intravenous formulation, diluted in sterile water and given orally, has been used successfully in infants with congenital heart disease [5].

MEDICATION SAFETY

Contraindications/Precautions

Contraindicated:[8].
- Anuria
- Hepatic coma until the condition is improved or corrected
- Severe electrolyte depletion until the condition is improved or corrected

Precautions:
Concomitant use: Use with lithium, probenecid, indomethacin, aminoglycosides, and drugs with ototoxic or nephrotoxic potential is not recommended [8].
Endocrine and metabolic: Hypokalemia may occur; therefore, use caution in patients on low-salt diets, receiving digitalis and diuretics for congestive heart failure, with hepatic cirrhosis and ascites, in states of aldosterone excess with normal renal function, potassium-losing nephropathy, certain diarrheal states, or other states where hypokalemia may add risks to the patient (eg, history of ventricular arrhythmias); monitoring and possible addition of potassium supplementation or potassium-sparing diuretics recommended [8].
Endocrine and metabolic: Hypocalcemia, hypomagnesemia, and hyperuricemia may occur; monitoring recommended [8].
Hematologic: Thrombocytopenia has been reported; monitoring recommended [8].
Hepatic: Sudden electrolyte alterations in patients with hepatic cirrhosis and ascites may precipitate hepatic encephalopathy and coma; initiation should be done on an inpatient basis with small doses and careful monitoring [8].
Immunologic: Patients with a sulfonamide allergy may show hypersensitivity to bumetanide [8].

Neurologic: Kernicterus could occur in critically ill or jaundiced neonates at risk for kernicterus; bumetanide displaces bilirubin [8].
Otic: Ototoxicity may occur, with an increased risk with IV therapy, frequent and high doses, and impaired renal function [8].
Renal: Reversible elevations in BUN and creatinine may occur, particularly in patients with dehydration and renal insufficiency [8].
Renal: Progressive renal disease with a marked increase in BUN or creatinine or development of oliguria; discontinue [8].

Adverse Effects

Water and electrolyte imbalances occur frequently, especially hyponatremia, hypokalemia, and hypochloremic alkalosis. Potentially ototoxic, but less so than furosemide. May displace bilirubin from albumin binding sites when given in high doses or for prolonged periods.

Black Box Warning

Bumetanide is a potent diuretic which, if given in excessive amounts, can lead to profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required, and dose and dosage schedule have to be adjusted to the individual patient's needs [8].

Solution Compatibility

D_5W and NS.

Terminal Injection Site Compatibility

Aztreonam, cefepime, furosemide, lorazepam, milrinone, morphine, piperacillin/tazobactam, and propofol.

Terminal Injection Site Incompatibility

Dobutamine and midazolam.

Monitoring

Serum electrolytes and urine output. Assess patients receiving digoxin concurrently for potassium depletion. Follow weight changes.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Bumetanide is a loop diuretic with a similar mechanism of action to furosemide. Inhibits chloride reabsorption in the ascending limb of Henle's loop and inhibits tubular sodium transport, causing major loss of sodium and chloride. Increases urinary losses of potassium, calcium, and bicarbonate. Urine sodium losses are lower with bumetanide than furosemide, but urine calcium losses are higher. Decreases CSF production by weak carbonic anhydrase inhibition. Decreases pulmonary transvascular fluid filtration. Increases renal blood flow and prostaglandin secretion. Highly protein bound (greater than 97%). Data from adults indicate excellent oral bioavailability and significant hepatic metabolism (40%) via the cytochrome CYP pathway. Serum half-life varies from 4 to 19 hours in neonates, determined by gestational age, postnatal age, and disease state.

ABOUT

Special Considerations/Preparation

Supplied as 2-, 4-, and 10-mL vials (0.25-mg/mL solution). Contains 1% (10 mg/mL) benzyl alcohol; pH adjusted to 7.
A 0.125-mg/mL dilution may be made by adding 3 mL of 0.25-mg/mL injectable solution to 3 mL preservative-free normal saline for injection. Refrigerated dilution is stable for 24 hours. Discolors when exposed to light.

There is no oral dosing formulation available for neonates. The intravenous formulation, diluted in sterile water and given orally, has been used successfully in infants with congenital heart disease [5].

DOSING/ADMINISTRATION

Dose

The dose varies with anesthetic procedure, the area to be anesthetized, the vascularity of the tissues, the number of neuronal segments to be blocked, the depth of anesthesia and degree of muscle relaxation required, the duration of anesthesia desired, individual tolerance, and the physical condition of the patient. Use the lowest dose and concentration to achieve the desired result [1][2]. The USES section provides dosage ranges; however, other resources should be consulted for specific techniques and procedures.

Dose Adjustments
Renal impairment: Select dose carefully since bupivacaine is excreted by the kidneys [3][2][1]
Hepatic impairment (moderate or severe): Consider reducing the dose with increased monitoring, especially with repeat doses [3][2][1]
Acutely ill and debilitated patients: Use a reduced doses commensurate with their age and physical status [3][2][1]
Methemoglobinemia: Discontinue use and manage medically [3][2][1]
Risk Factors for Seizures: When bupivacaine is administered by continuous infusion, reduce the rate in neonates who are at risk for seizures. Risk factors include increased uptake into the circulation (eg, pulmonary arteriovenous malformation) or lowered seizure threshold (eg, history of febrile convulsions during the postoperative period, hypomagnesemia, or hyponatremia due to free water overload) [4].

Uses

Epidural anesthesia: Epidural anesthesia, whether by caudal or lumbar route, is effective in the neonate [6]. Typical doses of bupivacaine 0.125% to 0.25% are 1.25 mg/kg to 2.5 mg/kg for caudal epidural anesthesia [7], 2 mg/kg up to a maximum of 2.5 mg/kg for epidural anesthesia (other than caudal route) [7][8][4], and 0.2 mg/kg/hr up to a maximum of 0.25 mg/kg/hr for continuous epidural infusion [7][8][9][4] for a maximum duration of 24 to 36 hours [9]. Data are lacking in premature infants. Although, one study used 3.125 mg/kg of 0.5% bupivacaine by the caudal route as an adjunct to general anesthesia in 20 premature infants (0 to 60 days; 520 to 2750 grams). No neonate experienced elevated heart rate or blood pressure at the time of incision [10]. In a retrospective analysis of 750 children (2 days to 16 years of age), bupivacaine 0.25% provided longer postoperative pain relief (up to 5 hours) than lidocaine 0.5% or 1.5% when administered caudally [11].

Peripheral nerve block: For neonatal circumcision a dorsal nerve block with a local anesthetic is recommended [7]. A penile nerve block is appropriate for urethral dilation and hypospadias repair [6]. Solutions containing epinephrine should NOT be used near end-artery

areas (eg, digits, nose, external ear, penis) or areas of compromised blood supply [12]. Efficacy data are lacking in neonates; however, in 2 pharmacokinetic studies bupivacaine nerve blocks were used in neonates without associated toxic concentrations or observed adverse events [13][14]. Doses of bupivacaine were 2 mg/kg for interpleural nerve block in 8 very low birthweight infants (700 g to 1022 g) [13] and 1.5 mg/kg for intercostal block in 11 full-term neonates (1 to 27 days of age) [14].

Spinal anesthesia: The use of spinal anesthesia is common in neonates, even preterm infants. In comparison to adults, the dose is greater in neonates [6]. Dose range is 0.5 to 1 mg/kg [6][15][16] with usual doses of 0.6 mg/kg of 0.75% hyperbaric bupivacaine in 8.25% dextrose [6][16] and 0.8 mg/kg of 0.5% isobaric bupivacaine [6]. The duration of effective spinal blockade (lack of hip flexion) was 84+/-16 minutes in 11 infants (range: 0.1 to 7 months of age; 2.8 to 9.3 kg) who received 0.75% bupivacaine 0.6 mg/kg in 8.25% dextrose solution with 0.02 mL of 1:1000 epinephrine [16]. Efficacy data are lacking in premature infants.

Pediatric FDA Approved Indications
Indicated for the production of local or regional anesthesia or analgesia for surgical procedures, dental and oral surgery procedures, and diagnostic and therapeutic procedures. Use is not recommended in pediatric patients younger than 12 years [3][2][1].
Marcaine™ Spinal: Indicated for production of subarachnoid block (spinal anesthesia). Use in patients younger than 18 years is not recommended [17].

Administration

Bupivacaine is **contraindicated** for intravenous regional anesthesia (Bier Block) [3][2][1].
Epidural anesthesia:
• Use only single-dose ampules and single-dose vials for caudal or epidural anesthesia as multiple dose vials contain a preservative [3][2].
• Administer slowly in 3- to 5-mL incremental doses with sufficient time between doses to detect signs/symptoms of unintentional intravascular or intrathecal injection [3][2]
• Perform syringe aspirations before and during each supplemental injection in continuous (intermittent) catheter techniques [3][2]
• Administer a test dose, which contains epinephrine, and monitor the effects prior to the full dose and with all subsequent doses when a catheter is in place [3][2][1]. The use of a local anesthetic in the test dose is probably unwarranted and may lead to toxicity [5].
• Avoid rapid injection of large volumes of anesthetic solutions. When possible, use fractional (incremental) doses [3][2][1].
Local infiltration and peripheral nerve blocks:
• Check aspiration for blood or cerebrospinal fluid (when applicable) prior to injecting any local anesthetic, both initial and subsequent doses [3][2][1].
• Avoid rapid injection of large volumes of anesthetic solutions. When possible, use fractional (incremental) doses [3][2][1].

MEDICATION SAFETY

Contraindications/Precautions

Contraindications

• Arrhythmias (eg, complete heart block) which severely restrict cardiac output (spinal injection) [17]
• Hypersensitivity to bupivacaine, to other amide-type anesthetics, or to any component of the product [25][17][3][2]
• Local infection at the site of proposed lumbar puncture (spinal injection) [17]
• Obstetrical paracervical block anesthesia [25][2][3]
• IV regional anesthesia (Bier Block) [25][2][19]
• Septicemia (spinal injection) [17]
• Severe hemorrhage (spinal injection) [17]
• Severe hypotension (spinal injection) [17]
• Shock (spinal injection) [17]

Precautions

Administration: Avoid intravascular injection; use proper technique (spinal injection) [17].
Administration: Risk of significant increase in plasma concentrations with repeated local administration [2].
Administration: Head and neck area (including retrobulbar, dental, and stellate ganglion blocks) administration has been associated with events that occur with systemic toxicity (convulsion, confusion, respiratory depression and/or respiratory arrest, and cardiovascular stimulation or depression); monitoring recommended [2].
Administration: Systemic toxicities, including CNS or cardiorespiratory depression and coma, leading to respiratory arrest, underventilation or apnea, have been reported with unintended intravascular or intrathecal injection [2]
Cardiovascular: Serious dose-related arrhythmias may occur with use of bupivacaine in combination with vasoconstrictors such as epinephrine during or after use of potent inhalation anesthetics [2].
Cardiovascular: Use caution in patients with a history of cardiac rhythm disturbances, shock, heart block, or hypotension [17].
Cardiovascular: Blood-flow restriction in end-artery areas (eg, digits, nose, external ear, penis) or areas of compromised blood supply may occur and cause ischemic injury or necrosis; increased risk in patients with hypertensive vascular disease [2].
Concomitant use: Avoid use of solutions containing antimicrobial preservatives (eg, multiple-dose vials) for epidural or caudal anesthesia [2].
Cardiovascular: Concomitant use with epinephrine or other vasopressors may increase risk of severe prolonged hypertension [2].
Concomitant use: Mixing or the prior or concurrent use of any other local anesthetic is not recommended for spinal injection [17].
Endocrine and metabolic: Familial malignant hyperthermia may be triggered by anesthetics; supportive therapy may be required [17].
Gastrointestinal: Inadvertent trauma to tongue, lips, and buccal mucosa may occur when used for dental injections [25].
Hematologic: Methemoglobinemia has been reported with use of local anesthetics; increased risk in patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites and other drugs associated with methemoglobinemia; if use is required in at-risk patients monitoring is

recommended. Medical management and discontinuation of therapy is required [2].
Hepatic: Increased risk of developing toxic plasma concentrations in patients with severe hepatic disease, especially with repeat doses; monitoring recommended and dosage adjustment may be required [2].
Immunologic: Bupivacaine with epinephrine solutions contain sodium metabisulfite; patients with sulfite sensitivity may experience allergic-type reactions including anaphylaxis and life-threatening or less severe asthmatic episodes in certain susceptible people [25]
Musculoskeletal: Chondrolysis has been reported with postoperative intra-articular infusions of local anesthetics (unapproved use) [2].
Neurological: Dose-related neurotoxicity may occur; delay in proper management, underventilation from any cause, or altered sensitivity may result in acidosis, cardiac arrest, and death. Monitoring recommended [2]
Renal: Increase risk of toxic reactions in patients with renal impairment; monitoring recommended [17].
Reproductive: Spinal anesthetics should not used during uterine contractions [17].
Respiratory: Respiratory arrest has been reported during retrobulbar blocks following local anesthetic injection; monitoring recommended [2].
Respiratory: Upper airway obstruction, requiring intubation; pulmonary edema; and tachydysrhythmia may occur with inadvertent vagal blockade in patients undergoing glossopharyngeal nerve block with bupivacaine for pain relief after tonsillectomy [26]. Vocal cord paralysis is a potential complication when bupivacaine is infiltrated in the peritonsillar region [27].
Special populations: Debilitated and acutely ill patients may have lower tolerance to elevated blood levels; dose adjustment recommended [3].

Adverse Effects

As with other amide-type local anesthetics, adverse effects are related to excessive concentrations due to overdosage, inadvertent intravascular injection, or slow metabolism of bupivacaine. These adverse events are serious, typically dose-related, and generally affect the central nervous and cardiovascular system. Central nervous system reactions include restlessness, anxiety, dizziness, tinnitus, blurred vision, tremors, convulsions, drowsiness, unconsciousness, respiratory depression, nausea, vomiting, chills, and pupillary constriction. Cardiovascular reactions include depression of myocardium, decreased cardiac output, heart-block, hypotension, bradycardia, ventricular arrhythmias (ventricular tachycardia and ventricular fibrillation), and cardiac arrest [25][17][3][2].
Rare allergic reactions may occur. Risks with epidural and spinal anesthesia or nerve blocks near the vertebral column include underventilation or apnea with inadvertent subarachnoid injection; and hypotension secondary to loss of sympathetic tone and respiratory paralysis or underventilation when motor blockade extends cephaladly. Other risks of epidural and spinal anesthesia include urinary retention, fecal and urinary incontinence, loss of perineal sensation, persistent anesthesia, paraesthesia, weakness, paralysis of the lower extremities and loss of sphincter control, headache, backache, septic meningitis, meningismus, and cranial nerve palsies due to traction on nerves from loss of cerebrospinal fluid. Risk of other routes of anesthesia include persistent anesthesia, paresthesia, weakness, paralysis, all of which may have slow, incomplete, or no recovery [25][17][3][2].

In pharmacokinetic studies, no adverse events were reported in 11 neonates following intercostal nerve block with bupivacaine [14], 8 very low birthweight infants following interpleural nerve block with bupivacaine [13], or 20 newborns (including 18 premature neonates) administered spinal anesthesia with bupivacaine [15].

Black Box Warning

There have been reports of cardiac arrest with difficult resuscitation or death during use of bupivacaine for epidural anesthesia in obstetrical patients. In most cases, this has followed use of the 0.75% (7.5 mg/mL) concentration. Resuscitation has been difficult or impossible despite apparently adequate preparation and appropriate management. Cardiac arrest has occurred after convulsions resulting from systemic toxicity, presumably following unintentional intravascular injection. The 0.75% (7.5 mg/mL) concentration of bupivacaine hydrochloride injection is not recommended for obstetrical anesthesia and should be reserved for surgical procedures where a high degree of muscle relaxation and prolonged effect are necessary [2][3].

Solution Compatibility

D_5W, NS.

Compatibility information refers to physical compatibility and is derived from Trissel's™ 2 Clinical Pharmaceutics Database. The determination of compatibility is based on concentrations for administration recommended herein. Drug compatibility is dependent on multiple factors (eg, drug concentrations, diluents, storage conditions). This list should not be viewed as all-inclusive and should not replace sound clinical judgment. The user is referred to Trissel's™ 2 for more complete details.

Monitoring

Therapeutic Physical Monitoring

• Monitor the level of anesthesia, which is not always controllable with spinal techniques (spinal injection) [18].

Toxic Laboratory Monitoring

• Closely monitor for signs and symptoms of methemoglobinemia in at-risk patients (eg, glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites) [19].

• In general, monitoring bupivacaine concentrations is not warranted; however, when there is a concern for accumulation then it may be appropriate. Consider monitoring concentrations when a local anesthesia is administered by continuous infusion at doses greater than 0.5 mg/kg/hr [20].

Toxic Physical Monitoring

• Monitor cardiovascular vital signs (heart rate and blood pressure) continuously after each local anesthetic injection [18][21][22]; especially blood pressure during the early phases of anesthesia in the elderly [18].
• Closely monitor for signs and symptoms of methemoglobinemia in at-risk patients (eg, glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites) [19].
• Monitor respiratory vital signs for adequate ventilation continuously after each local anesthetic injection [18][21][22].
• Monitor the patient's state of consciousness continuously after each local anesthetic injection [18][21][22].
• Monitor continuously for systemic toxicity including confusion, convulsions, respiratory depression or arrest, and cardiovascular stimulation or depression following retrobulbar, dental, ophthalmic, and stellate ganglion blocks [21][22]. Continuously monitor for level of pain control, using an appropriate pain assessment tool [7][23].
• Monitor heart rate and blood pressure, and check for circumoral pallor, palpitations, and nervousness following epidural anesthesia test dose [21][22].
• Test the level of anesthesia at T5-6 every 2 hours during epidural administration .[24].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Bupivacaine is a local anesthetic agent. It acts by blocking the conduction and generation of nerve impulses, probably by increasing the threshold that produces electrical excitation in the nerve, by reducing the rate of rise of the action potential, and by slowing the nerve impulse propagation. Systemic absorption depends on total dose and concentration, route of administration, vascularity of administration site, and presence or absence of epinephrine in the anesthetic solution. Onset of action is rapid. Compared with other local anesthetics, the duration of bupivacaine is longer. Analgesia persists beyond the return of sensation. Protein binding: 95%. Distributed to some extent to all body tissue, with the highest concentrations in highly perfused organs. After regional block, time to peak is 30 to 45 minutes, followed by a decline to insignificant levels during the next 3 to 6 hours. Metabolized primarily in the liver via conjugation with glucuronic acid. Mainly excreted through kidney; 6% excreted unchanged in the urine. Half-life is 2.7 hours and 8.1 hours in adults and neonates, respectively [25][17][3][2]. The bupivacaine concentrations considered toxic are 2 to 4 mg/mL [7].

Unbound bupivacaine did not accumulate in neonates and young infants (postmenstrual age, 40 to 59 weeks) administered single epidural injection (n=6; 1.5 mg/kg of 0.25%) and continuous epidural infusion (n=5; 0.2 mg/kg/hr starting 2 hours after single-injection). The median Cmax of unbound bupivacaine was 0.024 mg/L (0.013 to 0.12 mg/L) after a single injection and 0.052 mg/L (0.015 to 0.08 mg/L) after a continuous infusion; the corresponding values for total bupivacaine were 0.55 mg/L (0.37 to 1.61 mg/L) and 0.88 mg/L (0.58 to 1.91 mg/L), respectively [8]. Free bupivacaine concentrations were not elevated in 20 newborns

(including 18 premature neonates) administered spinal anesthesia with 0.5% isobaric bupivacaine 1 mg/kg with or without epinephrine 1:200,000. Total and free bupivacaine concentrations were 0.31+/-0.17 mcg/mL and 0.047+/-0.032 mcg/mL, respectively, for the without epinephrine group and 0.25+/-0.09 mcg/mL and 0.062+/-0.025 mcg/mL, respectively, for the with epinephrine group [15]. The volume of distribution, half-life, clearance, and peak concentration were 4.67 L/kg, 453 minutes, 7.9 mL/kg/min, and 0.52 mcg/mL, respectively, in 8 very low birthweight infants (700 g to 1022 g) after interpleural nerve block with bupivacaine 2 mg/kg [13]. In comparison with 11 full-term neonates (1 to 27 days of age) administered intercostal block with 1.5 mg/kg bupivacaine 0.25% , the values were 2.56 L/kg, 132 minutes, 16.93 mL/kg/min, and 0.82 mcg/mL, respectively [14].

ABOUT

Special Considerations/Preparation

Marcaine™: Available as 0.25% (2.5 mg/mL), 0.5% (5 mg/mL), and 0.75% (7.5 mg/mL) of bupivacaine in 10-mL and 30-mL single-dose vials (0.25%, 0.5%, and 0.75% strengths) without methylparaben and 50-mL multidose vials (0.25% and 0.5% strengths) containing methylparaben as a preservative. May be autoclaved at 15-pound pressure, 121 degrees C (250 degrees F) for 15 minutes [3].
Marcaine™ with epinephrine 1:200,000: Available as 0.25% (2.5 mg/mL) of bupivacaine in 10-mL and 30-mL single-dose vials and a 50-mL multidose vial and as 0.5% (5 mg/mL) of bupivacaine in 10-mL and 30-mL single-dose vials, and a 50-mL multidose vial. Each mL also contains 0.0091 mg of epinephrine and 0.5 mg of sodium metabisulfite. Multidose vials contain methylparaben as a preservative. Do not autoclave. Protect from light [25].
Marcaine™ Spinal: Available as 2-mL single-dose ampules containing 15 mg of bupivacaine and 165 mg of dextrose. May be autoclaved once at 15-pound pressure, 121 degrees C (250 degrees F) for 15 minutes. Does not contain preservatives [17].
Marcaine™ products should be stored at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F); excursions permitted between 15 and 30 degrees C (59 and 86 degrees F) [28]. Discard unused portion of solution in single-dose vials [3] and ampules [17].
Sensorcaine®: Available as 0.25% and 0.5% of bupivacaine in 50-mL multidose vials. Each mL contains 1 mg methylparaben (preservative) [2].
Sensorcaine®- methylparaben free (MPF): Available as 0.25%, 0.5%, and 0.75% of preservative-free bupivacaine in 10-mL and 30-mL single-dose vials [1].
Sensorcaine® with epinephrine 1:200,000: Available as 0.25% and 0.5% of bupivacaine in 50-mL multidose vials. Each mL contains 0.005 mg epinephrine, 0.5 mg sodium metabisulfite, and 1 mg methylparaben (preservative). Protect from light [29].
Sensorcaine®-MPF with epinephrine 1:200,000: Available as 0.25% (10-mL and 30-mL single-dose vials), 0.5% (10-mL and 30-mL single-dose vials), and 0.75% (30-mL single-dose vial) of preservative-free bupivacaine. Each mL contains 0.005 mg epinephrine and 0.5 mg sodium metabisulfite. Protect from light [30].
Sensorcaine® products should be stored at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F). Protect from light [29][30].

Also available as a 100 mg bupivacaine hydrochloride (equivalent to 88.8 mg bupivacaine) implant; each collagen implant is white to off-white in color and is approximately 5 cm x 5 cm x 0.5 cm in size. Store between 20 and 25 degrees C (68 and 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F). Protect from moisture and avoid contact with liquids prior to placement. Avoid excessive handling and compression of implant. Brief exposure to temperatures up to 40 degrees C (104 degrees F) may be tolerated provided the mean kinetic temperature does not exceed 25 degrees C (77 degrees F); however, such exposure should be minimized [31].

Buprenorphine

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Neonatal abstinence syndrome: Initial dose, 15.9 mcg/kg/day sublingually in 3 divided doses, **Maximum 60 mcg/kg/day** and **Maximum number of up-titrations = 6.**. Titrate dose up in 25% increments. Taper in 10% decrements until the dose is 10% of the initial dose, then discontinue [1][2][3][4].

Uses

Neonatal abstinence syndrome (NAS): Buprenorphine would be a reasonable choice for NAS if the neonate was exposed prenatally to buprenorphine [5].
Sublingual buprenorphine was associated with the largest reduction in length of treatment and length of stay for NAS in a network meta-analysis of 18 randomized controlled trials (n=1072) of buprenorphine, clonidine, diluted tincture of opium and clonidine, diluted tincture of opium, morphine, methadone, and phenobarbital. Morphine was the least effective opioid [6]. The findings should be interpreted with caution due to significant study limitations [6][7]
Compared with Methadone or Morphine: There was a 3-day reduction in the length of treatment with sublingual buprenorphine compared with conventional opioids (either morphine or methadone) in an observational trial of 360 infants (34 weeks or longer gestation) with NAS. Opioid treatment duration was 7.4 days (6.3 to 8.5 days) in the buprenorphine group compared with 10.4 days (9.3 to 11.5 days; p less than 0.001) in the conventional opioid group and the length of stay was 12.4 days (11.3 to 13.6 days) and 15.2 days (14.1 to 16.4 days; p less than 0.001), respectively. These reductions were consistent across the different types of intrauterine opioid exposure (short-acting opioids, methadone, buprenorphine, or combination of types). The initial dosage of buprenorphine was 4.5 mcg/kg/dose sublingual every 8 hours; with titrations/tapering of 1.5 mcg/kg/dose. Clonidine and/or phenobarbital were optional adjunct agents [8].
Compared with Methadone: A shorter duration of opioid treatment (9.4 vs 14 days) and shorter length of inpatient stay (16.3 vs 20.7 days) with a sublingual buprenorphine protocol compared with oral methadone protocol was demonstrated in a retrospective analysis of 201 infants (34 weeks' gestation or older) with NAS. Infants exposed in utero to methadone were excluded [9].
Compared with Morphine: Sublingual buprenorphine reduced the duration of treatment for neonatal abstinence syndrome compared with oral morphine (15 days vs 28 days; p less than 0.001) in a double-blind, double-dummy, single-center study (n=63). Preterm infants and infants exposed to benzodiazepines in utero were excluded. Median length of hospital stay was 21 vs 33 days (p less than 0.001) and use of supplemental phenobarbital was 15% vs 23% (p=0.36) for buprenorphine and morphine, respectively. Rates of adverse events were not different between the 2 groups [1].

Administration

After administration sublingually, place a pacifier in the infant's mouth. For a volume of the dose greater than 0.5 mL, give in 2 administrations separated by at least 2 minutes [1].

MEDICATION SAFETY

Contraindications/Precautions

Contraindicated with significant respiratory depression, acute or severe bronchial asthma (in an unmonitored setting or in the absence of resuscitative equipment), or known or suspected gastrointestinal obstruction (including paralytic ileus) [11].
Addiction potential: Opioid-type physical dependence may occur [12]
Alcoholism: Use cautiously in patients with acute alcoholism and delirium tremens [11]
Cardiovascular: QTc prolongation has been reported [11]
Cardiovascular:: Avoid use in patients with a history of long QT Syndrome, or an immediate family member with the syndrome [11]
Cardiovascular: Severe orthostatic hypotension and syncope in ambulatory patients may occur, especially in patients with compromised ability to maintain blood pressure [11][13][12], and in patients with reduced blood volume, or with concurrent administration of CNS depressants (eg, general anesthetics, phenothiazines) [11]
Cardiovascular: Avoid use in patients with circulatory shock [11].
Concomitant Use: Avoid use with Class 1A antiarrhythmic medications (eg, quinidine, procainamide, disopyramide) or Class 3 antiarrhythmic medications (eg, sotalol, amiodarone, dofetilide), or other medications that prolong the QT interval [11].
Concomitant Use: Patients requiring acute pain management or anesthesia are at risk. use non-opioid analgesia when possible; if opioid needed treat with high-affinity full opioid analgesia under supervision of physician with particular attention to respiratory function. Higher doses may be required. Use extreme care when using opioids as part of anesthesia [13].
Concomitant use: Concomitant use with benzodiazepines or other CNS depressants may result in an increased risk for overdose, death; monitoring and dose adjustment recommended. Consider prescribing naloxone for the emergency treatment of opioid overdose [14]
Dermatologic: Use implant with caution in patients with history of keloid formation or connective tissue disease (eg, scleroderma) [13].
Endocrine and metabolic: Use with caution in patients with myxedema, hypothyroidism, or adrenal cortical insufficiency [11][13][12].
Endocrine and metabolic: Adrenal insufficiency may occur with opioids. If suspected, perform diagnostic testing. If confirmed wean patient off of opioid if appropriate, treat with corticosteroids, and continue to assess adrenal function [11][13][15]
Gastrointestinal: Use may obscure diagnosis or clinical course in patients with acute abdominal conditions [13][12].

Gastrointestinal: Severe constipation may occur [11]
Hepatic: Sphincter of Oddi spasm may occur with morphine use [11]
Hepatic: Use caution with severe hepatic impairment [11]
Hepatic: Use cautiously in patients with biliary dysfunction [11]
Hepatic: Cytolytic hepatitis, hepatitis with jaundice, and hepatotoxicity, sometimes fatal, has been reported, with an increased risk with pre-existing liver enzyme abnormalities, comorbid hepatitis B or C virus, concomitant hepatotoxic drugs, or IV drug abuse [13]
Hepatic: Avoid use with preexisting moderate to severe hepatic impairment and discontinuation may be necessary if this occurs during treatment (subdermal implants) [13]
Hepatic: Increased intracholedochal pressure has been reported. Use cautiously in patients with biliary dysfunction [12]
Immunologic: Anaphylactic shock, bronchospasm, and angioneurotic edema has been reported [13][12]
Immunologic: Hypersensitivity reactions (eg, pruritus, rashes, hives) have been reported [13] including acute and chronic reactions [11]
Immunologic: Infection may occur at site of implant insertion or removal. Increased risk with excessive palpation after insertion and improper removal [13]
Immunologic: Use implant with caution in patients with history of recurrent MRSA infections [13].
Musculoskeletal: Use cautiously with kyphoscoliosis [11]
Musculoskeletal: Use implant with caution in patients with kyphoscoliosis [13].
Neurologic: Elevation of cerebrospinal fluid (CSF) pressure may occur and interfere with evaluation of patients with head injuries, intracranial lesions, or other conditions that increase CSF pressure [12]
Neurologic: Increased intracranial pressure may occur in susceptible patients (eg, brain tumors or head injury) due to decreased respiratory drive and carbon dioxide retention [11]
Neurologic: Avoid use with impaired consciousness or coma [11].
Neurologic: Use implant with caution in patients with CNS depression or coma [13][12]
Neurologic: New or worsening seizures may occur [11]
Neurologic: Potentially life-threatening serotonin syndrome may occur, particularly with concomitant use of serotonergic drugs [11][15].
Opioid overdose: Consider prescribing naloxone for the emergency treatment of opioid overdose based on the patient's risk factors for overdose (eg, concomitant use of CNS depressants, history of opioid use disorder, or prior opioid overdose) and if the patient has household members (including children) or other close contacts at risk for accidental exposure or overdose [14].
Psychologic: Use with caution in patients with toxic psychoses, acute alcoholism, or delirium tremens [13][12].
Psychologic: Use with caution in patients with toxic psychoses [11]
Renal: Use with caution in prostate hypertrophy or urethral stricture [11][13][12]
Renal: Use caution with severe renal impairment [11].
Reproductive: Long-term use of opioids may be associated with decreased sex hormone levels and symptoms such as reduced interest in sex, impotence, or infertility. Laboratory evaluation may be warranted [15].
Respiratory: Increased risk for further respiratory depression, particularly during treatment initiation and titration in patients with chronic pulmonary disease or otherwise impaired respiration [13][12]
Respiratory: Life-threatening respiratory depression may occur, especially with concomitant use of benzodiazepines or other CNS depressants [11][13][12] and particularly in the elderly, cachectic, or debilitated patients, those with chronic obstructive pulmonary disease or cor

pulmonale, and patients with substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression [11].
Respiratory: Sleep-related breathing disorders including central sleep apnea and sleep-related hypoxemia may occur and risk increases in a dose-dependent fashion; dose reduction may be necessary [16].
Special populations: Mental or physical impairment may occur, especially when beginning treatment or adjusting dosage. Avoid driving or operating dangerous machinery [12].
Special populations: Fatal respiratory depression may occur in children who are accidentally exposed to buprenorphine. Keep expelled implants away from children [13][12].
Special populations: Use implant with caution in debilitated patients [13].
Withdrawal: Abrupt withdrawal may result in severe withdrawal symptoms and should be avoided [13][12].

Adverse Effects

No buprenorphine-related adverse effects were reported in 2 open-label trials (n=50) [3][4].

Black Box Warning

There are serious risks, including profound sedation, respiratory depression, coma, and/or death, associated with combined use of opioids and benzodiazepines, other drugs that depress the CNS, or alcohol. Concomitant use should be reserved for patients with no alternative treatment. If necessary, use the lowest initial dose and titrate based on clinical response. Monitor patients closely for sedation and respiratory depression. Screen patients for risk of substance-use disorders [10].

Solution Compatibility

D_5W, D_5NS, NS, LR

Terminal Injection Site Compatibility

Buprenorphine 0.04 mg/mL: Acyclovir sodium (7 mg/mL), allopurinol (3 mg/mL), aminocaproic acid (20 mg/mL), amiodarone hydrochloride (3 mg/mL), amphotericin B lipid complex (1 mg/mL), amphotericin B liposome (1 mg/mL), anidulafungin (0.5 mg/mL), argatroban (1 mg/mL), atenolol (0.5 mg/mL), azithromycin (2 mg/mL), aztreonam (40 mg/mL), bivalirudin (5 mg/mL), capreomycin sulfate (10 mg/mL), cefepime hydrochloride (20 mg/mL), cisatracurium besylate (0.1 mg/mL), cytarabine (25 mg/mL), daptomycin (10 mg/mL), dexmedetomidine HCl (4 mcg/mL), diltiazem HCl (5 mg/mL), dolasetron mesylate (2

mg/mL), ertapenem sodium (20 mg/mL), fenoldopam mesylate (80 mcg/mL), filgrastim (30 mcg/mL), foscarnet sodium (24 mg/mL), fosphenytoin sodium (20 mg/mL), gatifloxacin (2 mg/mL), granisetron HCl (50 mcg/mL), hetastarch 6% (Hextend), lepirudin (0.4 mg/mL), leucovorin calcium (2 mg/mL), levofloxacin (5 mg/mL), linezolid (2 mg/mL), lorazepam (0.5 mg/mL), methotrexate sodium (15 mg/mL), metronidazole (5 mg/mL), milrinone lactate (0.2 mg/mL), mivacurium chloride (0.5 mg/mL), mycophenolate mofetil HCl (6 mg/mL), nesiritide (6 mcg/mL), nicardipine HCl (0.1 mg/mL), octreotide acetate (5 mcg/mL), palonosetron HCl (50 mcg/mL), pamidronate disodium (0.3 mg/mL), pancuronium bromide (0.1 mg/mL), pemetrexed disodium (20 mg/mL), piperacillin sodium-tazobactam sodium (40 mg/mL and 5 mg/mL), potassium acetate (0.2 mEq/mL), propofol (10 mg/mL), quinupristin-dalfopristin (5 mg/mL), remifentanil HCl (0.25 mg/mL), rocuronium bromide (1 mg/mL), sodium acetate (0.04 mEq/mL), tacrolimus (20 mcg/mL), teniposide (0.1 mg/mL), tigecycline (1 mg/mL), tirofiban HCl (0.1 mg/mL), vecuronium bromide (1 mg/mL), voriconazole (4 mg/mL), zoledronic acid (40 mcg/mL)

Buprenorphine 0.15 mg/mL: Alfentanil hydrochloride (0.25 mg/mL), amikacin sulfate (20 mg/mL), ascorbic acid injection (250 mg/mL), atracurium besylate (5 mg/mL), atropine sulfate (0.5 mg/mL), benztropine mesylate (0.5 mg/mL), bretylium tosylate (40 mg/mL), bumetanide (0.125 mg/mL), butorphanol tartrate (1 mg/mL), calcium chloride (50 mg/mL), calcium gluconate (50 mg/mL), cefamandole nafate (333 mg/mL), cefazolin sodium (220 mg/mL), cefoperazone (80 mg/mL), cefotaxime (285 mg/mL), cefotetan disodium (400 mg/mL), cefoxitin (450 mg/mL), ceftazidime (400 mg/mL), ceftizoxime (400 mg/mL), ceftriaxone sodium (165 mg/mL), cefuroxime (125 mg/mL), chloramphenicol sodium succinate (333 mg/mL), chlorpromazine HCl (4 mg/mL), cimetidine HCl (24 mg/mL), clindamycin phosphate (48 mg/mL), cyanocobalamin (0.5 mg/mL), cyclosporine (2 mg/mL), dexamethasone sodium phosphate (12 mg/mL), digoxin (0.125 mg/mL), diphenhydramine HCl (25 mg/mL), dobutamine HCl (6.25 mg/mL), dopamine HCl (12.8 mg/mL), doxycycline hyclate (4 mg/mL), enalaprilat (0.625 mg/mL), ephedrine sulfate (12.5 mg/mL), epinephrine hydrochloride (0.5 mg/mL), epoetin alfa (5000 units/mL), erythromycin lactobionate (20 mg/mL), esmolol HCl (40 mg/mL), famotidine (5 mg/mL), fentanyl citrate (25 mcg/mL), fluconazole (2 mg/mL), gentamicin sulfate (6.4 mg/mL), glycopyrrolate (0.1 mg/mL), heparin sodium (160 units/mL), hydrocortisone sodium succinate (62.5 mg/mL), hydroxyzine HCl (25 mg/mL), imipenem-cilastatin sodium (5 mg/mL), inamrinone lactate (2.5 mg/mL), regular insulin (50 units/mL), isoproterenol HCl (80 mcg/mL), ketorolac tromethamine (15 mg/mL), labetalol HCl (2.5 mg/mL), lidocaine HCl (10 mg/mL), magnesium sulfate (250 mg/mL), mannitol (150 mg/mL), meperidine HCl (50 mg/mL), metaraminol bitartrate (4 mg/mL), methyldopate HCl (25 mg/mL), methylprednisolone sodium succinate (125 mg/mL), metoclopramide hydrochloride (2.5 mg/mL), metoprolol tartrate (0.5 mg/mL), midazolam HCl (2.5 mg/mL), minocycline hydrochloride (0.8 mg/mL), morphine sulfate (4 mg/mL), multiple vitamins injection (0.08 mL/mL), nafcillin sodium (250 mg/mL), nalbuphine HCl (10 mg/mL), naloxone HCl (16 mcg/mL), netilmicin sulfate (50 mg/mL), nitroglycerin (1.6 mg/mL), nitroprusside sodium (0.8 mg/mL), norepinephrine bitartrate (0.5 mg/mL), ondansetron HCl (1 mg/mL), oxacillin sodium (160 mg/mL), oxytocin (0.08 units/mL), papaverine HCl (15 mg/mL), penicillin G potassium (500,000 units/mL), penicillin G sodium (500,000 units/mL), pentamidine isethionate (24 mg/mL), pentazocine lactate (15 mg/mL), phentolamine mesylate (5 mg/mL), phenylephrine HCl (4 mg/mL), phytonadione (5 mg/mL), piperacillin sodium (320 mg/mL), polymyxin B sulfate (0.667 mg/mL), potassium chloride (1 mEq/mL), procainamide HCl (250 mg/mL), prochlorperazine edisylate (2.5 mg/mL), promethazine HCl (25 mg/mL), propranolol HCl (0.5 mg/mL), protamine sulfate (5 mg/mL), pyridoxine HCl (50 mg/mL), quinidine gluconate (40 mg/mL), ranitidine HCl (2 mg/mL), streptokinase (80,000

units/mL), succinylcholine chloride (8 mg/mL), sufentanil citrate (25 mcg/mL), theophylline (4 mg/mL), thiamine HCl (50 mg/mL), ticarcillin disodium (345 mg/mL), ticarcillin disodium-clavulanate potassium (195 mg/mL), tobramycin sulfate (6.4 mg/mL), tolazoline HCl (12.5 mg/mL), urokinase (50,000 units/mL), vancomycin HCl (20 mg/mL), vasopressin (4 units/mL), verapamil HCl (1.25 mg/mL)

Buprenorphine 0.3 mg/mL: Acetaminophen (10 mg/mL)

Terminal Injection Site Incompatibility

Aminophylline (12.5 mg/mL), amphotericin B cholesteryl (0.83 mg/mL), ampicillin sodium (80 mg/mL), azathioprine sodium (13.33 mg/mL), dantrolene sodium (0.8 mg/mL), diazepam (2.5 mg/mL), diazoxide (7.5 mg/mL), indomethacin sodium trihydrate (1 mg/mL), lansoprazole (0.55 mg/mL), pantoprazole sodium (0.4 mg/mL), pentobarbital sodium (25 mg/mL), phenobarbital sodium (65 mg/mL), phenytoin sodium (25 mg/mL), sodium bicarbonate (0.5 mEq/mL), sulfamethoxazole-trimethoprim (20 mg/mL and 4 mg/mL)

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action: Buprenorphine hydrochloride, a narcotic analgesic, is a partial mu-opioid receptor agonist and an antagonist at the kappa-opioid receptor. Lower propensity for physical dependence and longer duration of action compared with morphine [17].

Pharmacokinetics - Pharmacodynamics: Higher average concentrations (C_{avg}) of buprenorphine were associated with shorter time to neonatal abstinence stabilization in a study of 28 neonates (37 weeks or more gestation; mean birth weight, 3.1 kg) exposed primarily to methadone *in utero*. No respiratory depression was observed. A dose of 15 mcg/kg/dose SL every 8 hours was predicted to achieve a target buprenorphine C_{avg} of 0.8 ng/mL; for some neonates 10 mcg/kg/dose may be sufficient and others 20 mcg/kg/dose may be necessary [18].

Plasma concentrations of buprenorphine ranged from less than 0.1 ng/mL (35.6% of samples) to 0.6 ng/mL with high intra-subject variability in 13 term infants administered buprenorphine (13.2 to 39 mcg/kg/day) sublingually. There were 3 out of 202 samples that were outliers. An infant receiving the starting dose of 13.2 mcg/kg/day had a level of (3.69 ng/mL). The outlier values of, 1.8 ng/mL, and 0.85 ng/mL occurred in 1 patient receiving the maximum protocol specified dose of 39 mcg/kg/day [4].

Bioavailability: Sublingual, neonates: 7% in a retrospective population pharmacokinetic analysis of 24 neonates with neonatal abstinence syndrome. Median gestational age in the neonates was 39.2 weeks (range, 36.6 to 41.2 weeks) and median weight was 2.9 kg (range, 2.2 to 4.1 kg) [19].

Protein binding: approximately 96% protein bound (primarily alpha and beta globulin) [17].
Vd: Sublingual: 142 L in 28 neonates (37 weeks or more gestation; mean birth weight, 3.1 kg) [18]
Metabolism: N-dealkylation, mediated primarily to CYP3A4, to norbuprenorphine as well as glucuronidation. Norbuprenorphine can undergo further glucuronidation [17].
Clearance: Sublingual: 3.5 L/hr/kg in a neonate (postnatal age, 5.4 days; weighing a median of 2.9 kg) [19]; 203 L/hr in 28 neonates (37 weeks or more gestation; mean birth weight, 3.1 kg) [18]
Elimination half-life: predicted half-life was 11 hours for sublingual buprenorphine in a retrospective population pharmacokinetic analysis of 24 neonates with neonatal abstinence syndrome and 5 adults (for model development). Median gestational age in the neonates was 39.2 weeks (range, 36.6 to 41.2 weeks) and median weight was 2.9 kg (range, 2.2 to 4.1 kg). Phenobarbital did not affect the clearance of buprenorphine. [19]. 31 to 35 hours [17].

ABOUT

Special Considerations/Preparation

Sublingual route
A 0.075 mg/mL (75 mcg/mL) buprenorphine solution was compounded by mixing buprenorphine for injection in 100% ethanol USP (30% total volume) and simple syrup USP (85 gm sucrose/100 mL). The solution is stable for 30 days at room temperature when stored in glass bottles and 7 days at room temperature when stored in syringes [20][3].

DOSING/ADMINISTRATION

Dose

Apnea of Prematurity
FDA-Approved Dosage (28 to less than 33 weeks gestation)
Loading dose: 20 mg/kg (1 mL/kg) IV over 30 minutes [1][2]
Maintenance dose: 5 mg/kg (0.25 mL/kg) IV over 10 minutes OR orally every 24 hours; initiate 24 hours after loading dose [1][2]

Off-label Dosage
22 to 28 weeks gestational age
Loading dose: Median, 20 mg/kg IV (range, 19 to 23 mg/kg) [3]
Maintenance dose: Median, 8 mg/kg/day (range 5 to 10 mg/kg/day) [3]
Duration of therapy: Median, 60 days (range 46 to 75 days) [3]

Dose Adjustment
Hepatic Impairment: Monitor serum caffeine concentrations and adjust dose as necessary to prevent toxicity [1][2].
Renal Impairment: Monitor serum caffeine concentrations and adjust dose as necessary to prevent toxicity [1][2].

Uses

High-dose therapy vs Standard-dose therapy:
A meta-analysis that include 7 studies (894 very preterm infants) found no significant difference in mortality rates or adverse effects when high-dose caffeine therapy was compared with standard-dose caffeine therapy (low certainty evidence), though high-dose therapy was associated with a significant reduction in rates of bronchopulmonary dysplasia (BPD; chronic lung disease) at 36 weeks post-menstrual age (moderate certainty evidence) [4].
• **Primary outcomes:** All-cause mortality was not significantly different with high-dose caffeine therapy compared with standard dose therapy when used for any indication (relative risk{[RR], 0.86; 95% CI, 0.53 to 1.38; 5 studies, 723 patients). Similar results were obtained when broken down by indication (treatment of apnea, prevention of apnea, or prevention of reintubation) [4]. Neurodevelopmental disability outcomes at 3 to 5 years of age were reported in 1 study (46 patients) and no significant differences were reported (very low certainty evidence) [4][5].
• **Secondary outcomes:** BPD was significantly reduced by 25% with high-dose caffeine therapy compared with standard-dose therapy when used for any indication (RR, 0.75; 95% CI, 0.6 to 0.94; 5 studies, 723 patients). When broken down by indication, the results were only significantly in favor of high-dose caffeine in those treated for prevention of

reintubation; findings were not significant for treatment or prevention of apnea [4].
• **Adverse effects:** There was no significant difference between treatment groups in rates of adverse effects leading to a dose reduction or discontinuation of therapy (eg, tachycardia, feeding intolerance, agitation; 5 studies, 593 patients). There was also no significant difference in seizures, though this result was from very low certainty evidence (1 study, 74 patients) [4],
• **Dosage regimens:** High dose regimens were defined as those with a loading dose greater than 20 mg/kg and maintenance dose greater than 10 mg/kg/day. Among the included studies, high-dose regimen loading doses ranged from 30 to 80 mg/kg and maintenance doses from 12 to 30 mg/kg/day. Standard dose regimens were defined as those with a loading dose of 20 mg/kg or less and a maintenance dose of 10 mg/kg/day or less. Among the included studies, standard-dose regimen loading doses ranges from 6 to 25 mg/kg and maintenance doses from 3 to 10 mg/kg/day [4].
• **Inclusion criteria and patient characteristics:** Randomized controlled trials (RCTs), quasi-RCTs, and cluster RCTs comparing high-dose and standard-dose caffeine regimens were included. Apnea prevention studies included preterm infants born at less than 34 weeks gestation at risk for apnea; apnea treatment studies included preterm infants born at less than 37 weeks gestation with signs of apnea; and studies for the prevention of reintubation included preterm infants born at less than 34 weeks gestation given caffeine prior to extubation [4].

High-dose therapy
A retrospective study of 410 infants 28 weeks gestational age (GA) or younger (median GA, 26 weeks) treated with caffeine citrate at higher doses and for longer durations than is FDA-approved (median loading dose, 20 mg/kg; median maintenance dose, 8 mg/kg/day; median duration, 60 days) reported the following [3]:
• Significantly reduced odds of necrotizing enterocolitis (NEC) with increased caffeine dose (odds ratio, 0.78; 95% CI, 0.63 to 0.92) [3]
• Significantly reduced odds of needing patent ductus arteriosus (PDA) ligation with increased caffeine dose (odds ratio, 0.74; 95% CI, 0.61 to 0.86) [3]
• No significant association between dose and bronchopulmonary dysplasia (BPD) [3]
• No significant association between increasing duration of therapy and BPD, NEC, or PDA ligation [3]
A significant reduction in extubation failure (22% vs 47%), the frequency of apnea (9 vs 16), and days of documented apnea (2.5 days vs 5 days) were observed with high-dose oral caffeine citrate compared with standard dose (20 mg/kg/day loading dose, 10 mg/kg/day maintenance) in a randomized, double-blind study in 120 preterm (less than 32 weeks gestation; 10 days or younger) with apnea of prematurity. Tachycardia was significantly more frequent (23% vs 8%) in the high-dose vs low-dose group [6].

Apnea: Pharmacological treatment with caffeine is the standard of care for apnea of prematurity [7].
The rate of bronchopulmonary dysplasia in neonates with apnea of prematurity was reduced with caffeine, started within the first 10 days of life, in a randomized, placebo-controlled trial (n=1917). Caffeine was started to prevent apnea, treat apnea, or to facilitate the removal of an endotracheal tube [8]. A follow-up of the study at 18 months corrected age demonstrated that the risk of death or disability (cerebral palsy, cognitive delay, severe hearing loss, and bilateral blindness) was reduced with caffeine [9]. At a 5-year follow-up, there was no difference in disability or death between the caffeine and placebo group [10]. At an 11-year follow-up, the combined rate of academic, motor, and behavioral impairment did not differ

between the caffeine and placebo group. There was a reduced risk of motor impairment with caffeine compared with placebo (adjusted OR 0.66 (95% CI, 0.48 to 0.9)) [11]. A secondary analysis (n=675) of a retrospective, multicenter cohort study demonstrated an association of less frequent early acute kidney injury in preterm neonates with caffeine administered by 7 days of life; 11.2% vs 31.6% with and without caffeine, respectively (adjusted odds ratio 0.2 (95% CI, 0.11 to 0.34)) [12].

Initiation: The optimal time to start treatment with caffeine is unknown. A reasonable approach is to start caffeine when apnea develops in infants greater than 28 weeks' gestation who do not require positive pressure support. Earlier (younger than 3 days) prophylactic caffeine in infants who require mechanical ventilation compared with later (3 days or older) has been studied but the safety and efficacy need further study [7]. Caffeine administered within the first 24 hours of life was associated with less mechanical ventilation (71.3% vs 83.2%) and a shorter duration of mechanical ventilation (mean 5 vs 10.8 days) than later caffeine initiation (median of 4 days) in an analysis of an observational study (n=286). Lower rates of patent ductus arteriosus and intraventricular hemorrhage (IVH) were associated with early versus late initiation; however, higher grades of IVH were not reduced. Premature infants (32 weeks' gestational age or less) with respiratory distress syndrome and treated with surfactant were included [13].

Duration: The optimal duration of treatment with caffeine is unknown. Consider a trial off of caffeine in infants who have been free of clinically significant apnea/bradycardia events after 5 to 7 days off positive pressure or at 33 to 34 weeks postmenstrual age, which ever comes first [7]. Extending caffeine treatment beyond when it is normally discontinued (apnea resolution) reduced the number and severity of intermittent hypoxia episodes in infants; however, the long-term benefits and risks to extended treatment are unknown. The postmenstrual age (PMA) at randomization to caffeine or placebo was 34 to 37 weeks (n=95) and continuous pulse oximeter data were collected up until 39 weeks PMA [14]. More studies are needed before implementing extended caffeine treatment beyond apnea resolution [7].

Mechanical Ventilation Weaning: The age at first successful extubation did not differ between early caffeine use (median 24 days of age; interquartile range (IQR), 10 to 41 days) and placebo group (median 20 days of age; IQR, 9 to 43 days; p=0.703) in preterm infants born at 23 to 30 weeks of gestation requiring mechanical ventilation in the first 5 postnatal days in a randomized, double-blind, placebo-controlled trial (n=83). Additionally, no differences were detected in secondary outcomes (duration of mechanical ventilation and oxygen supplementation, bronchopulmonary dysplasia, or death). The trial was terminated early due to a trend of higher mortality; 22% for caffeine and 12% (p=0.22) for placebo. The mean ages were approximately 3 hours at intubation and 2 days at randomization. The dosage for caffeine citrate was 20 mg/kg followed by 5 mg/kg/day [15].

Pediatric FDA-approved Use

Indicated for the short-term treatment of apnea of prematurity in infants between 28 to younger than 33 weeks of gestational age [2].

The use of caffeine for sudden infant death syndrome prophylaxis or prior to extubation in mechanically-ventilated infants has not been established [2].

Administration

Administer the IV loading dose over 30 minutes and the maintenance dose over 10 minutes [1]

MEDICATION SAFETY

Contraindications/Precautions

Precautions
Cardiovascular: Use with caution in infants with cardiovascular disease [1].
Gastrointestinal: Necrotizing enterocolitis has been reported; careful monitoring recommended [1].
Hepatic: Use with caution in infants with impaired hepatic function; monitoring recommended and dosage adjustment may be required [1].
Neurologic: Use with caution in infants with seizure disorders [1].
Renal: Use with caution in infants with impaired renal function; monitoring recommended and dosage adjustment may be required [1].

Adverse Effects

Common: Feeding intolerance (8.7% vs 5.1% with placebo); rash (8.7% vs 7.7%). Other reported adverse effects include CNS stimulation (restlessness, irritability), cardiovascular effects (tachycardia, increased left ventricular output), and renal effects (increased urine outflow, increased creatinine clearance, increased sodium and calcium excretion [1].
Serious: Necrotizing enterocolitis was reported in 5 patients exposed to caffeine (with 3 deaths) compared with 1 patient exposed to placebo (N=85). A larger study (N=2000) found no difference in the rate of necrotizing enterocolitis with caffeine compared with placebo [1].

Monitoring

Laboratory Monitoring
Concentration
•Measuring serum concentrations is probably not necessary [7].
•Obtain baseline caffeine levels in neonates previously treated with theophylline and neonates born to mothers who consumed caffeine prior to delivery [1].
•Monitor serum concentrations in the presence of renal or hepatic impairment [1].
•If monitoring of serum drug concentration is performed, measure the trough level on approximately day 5 of therapy. Therapeutic trough serum concentration is 5 to 25 mcg/mL. Concentrations greater than 40 to 50 mcg/mL are toxic [1].
Other Laboratory Values
•Periodically monitor serum glucose [1].

Physical Findings

•Watch for signs and symptoms of necrotizing enterocolitis [1].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of Action: Caffeine is structurally related to other methylxanthines, theophylline, and theobromine. It is a bronchial smooth muscle relaxant, a CNS stimulant, a cardiac muscle stimulant, and a diuretic. Although the mechanism action of caffeine in apnea of prematurity is not known, several mechanisms have been hypothesized. These include: (1) stimulation of the respiratory center, (2) increased minute ventilation, (3) decreased threshold to hypercapnia, (4) increased response to hypercapnia, (5) increased skeletal muscle tone, (6) decreased diaphragmatic fatigue, (7) increased metabolic rate, and (8) increased oxygen consumption. Most of these effects have been attributed to antagonism of adenosine receptors, both A_1 and A_2 subtypes, by caffeine, which has been demonstrated in receptor binding assays and observed at concentrations approximating those achieved therapeutically [1].

Therapeutic Drug Concentration
Peak concentration
•**Cmax, single-dose, 10 mg, preterm neonates:** 6 to 10 mg/mL [1]
Time to peak concentration
•**Tmax:** 30 minutes to 2 hours in preterm neonates [1]

Absorption
•**Effect of food:** Not affected by formula feeding[1]

Distribution
Tissue and Fluid Distribution:
• **Brain:** Rapidly distributed [1]
• **CSF:** Similar to plasma levels in preterm neonates [1]
Vd: 0.8 to 0.9 L/kg in infants [1]

Metabolism: Via CYP1A2; limited in preterm neonates due to immature hepatic enzymes. Approximately 3 to 8% of a dose in preterm neonates may convert to theophylline [1]

Excretion
•**Renal Elimination:** 86% as unchanged drug within 6 days of a dose in neonates; by 9 months about 1% is eliminated as unchanged drug (similar to adult values) [1]

Elimination Half-Life
•**Parent compound:** 3 to 4 days in neonates; by 9 months half-life is 5 hours (similar to adult values) [1]

ABOUT

Special Considerations/Preparation

Both injectable and oral caffeine citrate solutions are preservative free and available in 3-mL single use vials. Each mL contains 20 mg of caffeine citrate (equivalent to 10 mg caffeine base). Store at room temperature [1][2].

Extemporaneous compounds

Injectable solution 20 mg/mL caffeine citrate

Dissolve 10 g of **caffeine citrate** powder in 250 mL of sterile water for injection USP. Transfer the solution to a 500-mL empty evacuated container (EEC). Add sufficient sterile water for injection for a total volume of 500 mL. Filter the solution through a 0.22 micron filter set into an empty 500-mL EEC, then transfer the filtered solution into sterile, empty 10-mL vials. Autoclave the vials at 121 degrees Centigrade for 15 minutes and allow to cool. Quarantine the product until sterility and pyrogen testing are completed. Stable for 90 days under refrigeration [16].

Oral solution 20 mg/mL caffeine citrate

Dissolve 10 g of **caffeine citrate** powder in 250 mL of sterile water for irrigation USP. Add a 2:1 mixture of simple syrup and cherry syrup to make a total volume of 500 mL. Stable for 90 days under refrigeration [16].

Oral solution 10 mg/mL caffeine base (Note: 10 mg caffeine base = 20 mg of caffeine citrate)

Alternatively, an oral solution may be prepared by dissolving 2.5 g of **caffeine anhydrous** powder in 250 mL of water, yielding a final concentration of 10 mg/mL **caffeine base**. Solution is stable for 4 weeks refrigerated. Crystals form when stored at low temperature but dissolve at room temperature without loss of potency. **Do not freeze.**

Calcium - Oral

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Hypocalcemia, non-acute: 20 to 80 mg/kg/day elemental calcium orally in 2 to 4 divided doses scheduled around oral feedings.

Calcium gluconate 10% IV formulation (9.3 mg/mL elemental calcium): 2 to 8 mL/kg/day.
Calcium carbonate 250 mg/mL suspension (100 mg/mL elemental calcium): 0.2 to 0.8 mL/kg/day.
Calcium glubionate syrup (23 mg/mL elemental calcium): 1 to 3.5 mL/kg/day.

Rickets
Preterm neonates: Supplementation with 20 mg/kg/day of elemental calcium and 10 to 20 mg/kg/day of elemental phosphorus. Increase as tolerated, to a **maximum 70 to 80 mg/kg/day of elemental calcium and 40 to 50 mg/kg/day of elemental phosphorus** in preterm infants enterally fed [1]. Administer in 2 to 4 divided doses.

Calcium gluconate 10% IV formulation (9.3 mg/mL elemental calcium): 2 to 8 mL/kg/day.
Calcium carbonate 250 mg/mL suspension (100 mg/mL elemental calcium): 0.2 to 0.8 mL/kg/day.
Calcium glubionate syrup (23 mg/mL elemental calcium): 1 to 3.5 mL/kg/day.

Uses

Hypocalcemia, non-acute in babies able to tolerate oral medications.

Rickets: In enterally fed preterm infants with radiologic evidence of rickets, maximize nutrient intake by increasing human milk fortifier and/or volume of preterm formula. If maximization cannot be tolerated, then supplementation with elemental calcium and phosphorus is recommended. Vitamin D status should be evaluated and target 25-hydroxyvitamin D concentrations of greater than 20 ng/mL (50 nmol/L). The recommended intakes for enterally fed, very low birth weight infants are 150 to 220 mg/kg/day for calcium and 75 to 140 mg/kg/day for phosphorus [1].

MEDICATION SAFETY

Adverse Effects

Oral calcium preparations are hypertonic, especially calcium glubionate syrup. Gastric irritation and diarrhea occur often. Use with caution in infants who are at risk for necrotizing enterocolitis.

Monitoring

Periodically measure serum calcium concentrations. Assess GI tolerance. Assess serum phosphorus and vitamin D levels when indicated.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Absorption of calcium administered orally is approximately 50%. Absorption takes place throughout the small intestine, and is primarily regulated by 1,25-dihydroxy Vitamin D. Calcium carbonate significantly interferes with the absorption of levothyroxine. The osmolarity of calcium glubionate syrup is 2500 mOsm/L, and of calcium gluconate is 700 mOsm/L.

ABOUT

Special Considerations/Preparation

Calcium carbonate (Roxane) is available as a 250 mg/mL suspension (equivalent to 100 mg/mL elemental calcium) in 5-mL unit dose cups.

Calcium glubionate syrup 360 mg/mL (1.8 g/5 mL) (Rugby/Watson) yields 23 mg/mL elemental calcium (1.16 mEq/mL) and is available in 473 mL bottles. Osmolarity is 2500 mOsm/L.

Calcium Chloride

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

10% calcium chloride contains 100 mg/mL of calcium chloride which is equivalent to 27 mg/mL (1.4 mEq/mL) of elemental calcium [1].

Calcium Channel Blocker Toxicity: 20 mg/kg/dose calcium chloride (0.2 mL/kg calcium chloride 10%) IV/IO over 5 to 10 minutes **Maximum single dose 2 g**[2][3]; if initial dose is beneficial, may start an infusion at 20 to 50 mg/kg/hour (PALS guideline dosage) [3] or 20 to 40 mg/kg/hour, titrated to blood pressure [2].

Cardiac Resuscitation (Use only for documented hypocalcemia, hyperkalemia, or hypermagnesemia): 20 mg/kg/dose calcium chloride (0.2 mL/kg calcium chloride 10%) slow IV infusion over 30 to 60 minutes or IO. A central line is recommended [3][4]; **Maximum single dose 1 g** (AAP guideline dosage) [4].

Exchange transfusion: 33 mg calcium chloride 10% per 100 mL citrated blood exchanged (equals 0.33 mL per 100 mL blood exchanged). Infuse IV over 10 to 30 minutes.

Hypocalcemia:
Calcium gluconate given at the same elemental calcium dose may be preferred as calcium chloride may cause a metabolic acidosis[5][6]
FDA Dosage: 2.7 to 5 mg/kg IV of calcium chloride (0.027 to 0.05 mL/kg of 10% calcium chloride) MAX rate, 1 mL/min of 10% calcium chloride; no data on repeat doses but some experts recommend repeat doses every 4 to 6 hours (FDA dosage) [1].
Asymptomatic or mildly symptomatic hypocalcemia, or maintenance after achievement of normal calcium values after IV therapy: 40 to 80 mg/kg/day **elemental** calcium IV or orally in 3 to 4 divided doses (equivalent to 148 to 296 mg/kg/day calcium chloride) [7][8]; adjust to achieve a daily urinary calcium excretion of less than 4 mg/kg/day [7]
Symptomatic hypocalcemia: 10 to 20 mg/kg **elemental** calcium (equivalent to 37 to 74 mg/kg calcium chloride) IV over 10 to 30 minutes followed by continuous infusion of 50 to 80 mg/kg/day **elemental** calcium (equivalent to 185 to 296 mg/kg/day calcium chloride) for 48 hours. If calcium values are in normal range after 48 hours of continuous infusion, decrease infusion by 50% for the next 24 hours, then discontinue [7][8]

Uses

Calcium Channel Blocker (CCB) Toxicity: Administration of calcium is reasonable for CCB toxicity as improvements in heart rate, blood pressure, and conduction abnormalities have been reported. However, the available literature on calcium monotherapy for severe

CCB toxicity are limited, and most patients require additional treatment modalities. In one case series, high doses of calcium gluconate (targeting ionized calcium concentrations up to twice normal) appeared more effective than lower doses[2].

Cardiac Resuscitation: In newly born infants in a cardiac resuscitation setting, drugs are rarely needed [9][10]. Use calcium only in cases of documented hypocalcemia, hyperkalemia, hypermagnesemia, or calcium channel blocker toxicity. Routine use of calcium in cardiac resuscitation is not recommended. [11]. Calcium chloride or calcium gluconate may be used; but calcium chloride is preferred in cardiac arrest setting [3]. For hyperkalemia specifically, calcium will stabilize the cardiac cellular membrane but does not result in transcellular shift or excretion of potassium; another therapy that results in the shift of intracellular potassium or excretion of potassium is required [12]

Hypocalcemia [7][5][6]. Hypocalcemia, usually defined as a serum ionized calcium concentration less than 4.4 mg/dL (or total serum calcium less than approximately 8 mg/dL) for term and preterm infants weighing greater than 1500 g at birth and ionized calcium less than 4 mg/dL (or total calcium less than 7 mg/dL) for infants weighing less than 1500 g at birth. Treatment is suggested when serum calcium is less than 6 mg/dL in preterm infants and less than 7 mg/dL in term infants [7]. Calcium gluconate given at the same elemental calcium dose may be preferred as calcium chloride may cause a metabolic acidosis [5][6], though calcium chloride may be preferred in cases of severe hypocalcemia with poor cardiac function, as liver metabolism is not required for the release of free calcium [8]

FDA approve use: For hypocalcemia in those conditions requiring prompt increase in plasma calcium concentrations [1].

Administration

•Intravenous route only [1]; may also be administered by intraosseous [3].
•Not for IM, subQ [1], or endotracheal use[3], or by intra-arterial route [6].
•Administer slowly through a small needle in a large vein, preferably in a central or deep vein [1]. Central line is preferred but peripheral vein is acceptable in a cardiac arrest setting. In non-arrest setting, calcium gluconate is recommended [3].
•Warm solution to body temperature if time permits [1].
•Rate should not exceed 1 mL/min of a 100 mg/mL calcium chloride solution [1]. May be administered over 30 to 60 minutes [4] or may be diluted 1:1 with D5W and administered over 10 to 30 minutes [8].
•Avoid high concentrations of calcium from reaching heart due to risk of cardiac syncope [1].

MEDICATION SAFETY

Contraindications/Precautions

Contraindications

•Ventricular fibrillation [1]
•Risk of existing digitalis toxicity [1]

Precautions
Administration: Do not inject into tissue because severe necrosis and sloughing may occur [1]
Administration: Avoid extravasation or accidental injection into perivascular tissues [1]
Administration: Rapid administration is associated with bradycardia or cardiac arrest [13].
Concomitant Use: With digitalis drugs due to additive effect; use caution [1]
Renal: Patients with impaired renal function, including premature neonates, may experience aluminum toxicity with prolonged parenteral administration [1]

Adverse Effects

Precipitate in the infusion line with crystalline deposits in the lungs and kidneys has been reported in some deceased neonates who were coadministered ceftriaxone IV and calcium-containing fluids, sometimes in the same infusion line. At least one neonatal fatality has been reported following coadministration at different times and with separate infusion lines, though no crystalline deposits were found at autopsy in this neonate. These reports have been confined to neonates [14]. Cutaneous necrosis or calcium deposition occurs with extravasation. Bolus infusions by UAC have been associated with intestinal bleeding and lower-extremity tissue necrosis.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Amikacin, amiodarone, chloramphenicol, dobutamine, dopamine, epinephrine, esmolol, hydrocortisone, isoproterenol, lidocaine, micafungin, milrinone, morphine, penicillin G, pentobarbital, phenobarbital, prostaglandin E_1, and sodium nitroprusside.

Terminal Injection Site Incompatibility

Amphotericin B, ceftriaxone, sodium bicarbonate, and phosphate and magnesium salts when mixed directly.

Monitoring

Therapeutic Laboratory Monitoring

Monitor serum ionized calcium levels [1].
Measure calcium levels every 8 to 12 hours during continuous infusion until normal values achieved [7].

Therapeutic Physical Monitoring

Titrate dose to blood pressure when used to reverse calcium channel blocker toxicity [2]

Toxic Laboratory Monitoring

Continuous ECG monitoring is recommended during the acute management of hyperkalemia [12] or during bolus dose infusion for the treatment of acute hypocalcemia [7][8].
Do not exceed serum ionized calcium concentration 1.5 to 2 times the upper limits of normal when used to reverse calcium channel blocker toxicity [2]

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of Action: Calcium plays important physiological roles, many of which are poorly understood. It is essential for the functional integrity of the nervous and muscular systems. It is necessary for normal cardiac function and is one of the factors that operates in the mechanisms involved in the coagulation of blood. Calcium chloride in water dissociates the provide calcium (Ca^{++}) and chloride (Cl^{-}) ions. They are normal constituents of the body fluids and are dependent on various physiological mechanisms for maintenance of balance between intake and output [1]
Hyperkalemia: For hyperkalemia specifically, calcium will stabilize the cardiac cellular membrane but does not result in transcellular shift or excretion of potassium; another therapy that results in the shift of intracellular potassium or excretion of potassium is required [12]

Pharmacodynamics

Onset: Immediate [4]

Excretion

Renal Excretion: 20% [1]
Fecal Excretion: 80% as insoluble salts [1]

ABOUT

Special Considerations/Preparation

Calcium chloride 10% injection yields 27 mg/mL elemental calcium (1.36 mEq/mL). Osmolarity is 2040 mOsm/L. Injectable calcium salts should be stored at room temperature and are stable indefinitely [15].

Calcium Gluconate

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

10% calcium gluconate contains 100 mg/mL of calcium gluconate which is equivalent to 9.3 mg/mL (0.465 mEq/mL) of elemental calcium[1]

Calcium Channel Blocker Toxicity: Initial: 60 mg/kg calcium gluconate (0.28 mEq elemental calcium/kg) IV/IO **Maximum single dose 6 g**; maintenance 60 to 120 mg/hg/hr (0.28 to 0.56 mEq elemental calcium/kg/hr), titrated to blood pressure [2].

Cardiac Resuscitation (documented hypocalcemia, hyperkalemia, hypermagnesemia, or calcium channel blocker overdose): 60 to 100 mg/kg calcium gluconate slow IV push/IO; repeat dose as necessary for clinical effect (**MAX: 2000 mg/dose**) (guideline dosage) [3][4].

Hypocalcemia
Asymptomatic or mildly symptomatic hypocalcemia, or maintenance after achievement of normal calcium values after IV therapy: 40 to 80 mg/kg/day **elemental** calcium IV or orally in 3 to 4 divided doses (equivalent to 430 to 860 mg/kg/day calcium gluconate) [5][6]; adjust to achieve a daily urinary calcium excretion of less than 4 mg/kg/day [5].
Symptomatic Hypocalcemia: 10 to 20 mg/kg **elemental** calcium (equivalent to 100 to 200 mg/kg calcium gluconate) IV over 10 to 30 minutes followed by continuous infusion of 50 to 80 mg/kg/day **elemental** calcium (equivalent to 538 to 860 mg/kg/day calcium gluconate) for 48 hours [5][6][1]. If calcium values are in normal range after 48 hours of continuous infusion, decrease infusion by 50% for the next 24 hours, then discontinue [5][6].

Parenteral Nutrition
Daily Requirement
Preterm neonates: 2 to 4 **mEq**/kg/day IV of calcium [7].
Full-term neonates: 0.5 to 4 **mEq**/kg/day IV of calcium [7].

Exchange transfusion: 100 mg calcium gluconate 10% per 100 mL citrated blood exchanged (equals 1 mL per 100 mL blood exchanged). Infuse IV over 10 minutes.

Uses

Calcium Channel Blocker (CCB) Toxicity: Administration of calcium is reasonable for CCB toxicity as improvements in heart rate, blood pressure, and conduction abnormalities have been reported. However, the available literature on calcium monotherapy for severe CCB toxicity are limited, and most patients require additional treatment modalities. In one

case series, high doses of calcium gluconate (targeting ionized calcium concentrations up to twice normal) appeared more effective than lower doses[2].
Cardiac resuscitation: In newly born infants in a cardiac resuscitation setting, drugs are rarely needed [9][10]. Use calcium only in cases of documented hypocalcemia, hyperkalemia, hypermagnesemia, or calcium channel blocker toxicity. Routine use of calcium in cardiac resuscitation is not recommended. [11]. Calcium chloride or calcium gluconate may be used; but calcium chloride is preferred in cardiac arrest setting [4]. For hyperkalemia specifically, calcium will stabilize the cardiac cellular membrane but does not result in transcellular shift or excretion of potassium; another therapy that results in the shift of intracellular potassium or excretion of potassium is required [12].

Hypocalcemia [5][13][14]. Hypocalcemia, usually defined as a serum ionized calcium concentration less than 4.4 mg/dL (or total serum calcium less than approximately 8 mg/dL) for term and preterm infants weighing greater than 1500 g at birth and ionized calcium less than 4 mg/dL (or total calcium less than 7 mg/dL) for infants weighing less than 1500 g at birth. Treatment is suggested when serum calcium is less than 6 mg/dL in preterm infants and less than 7 mg/dL in term infants [5]. Calcium gluconate is generally preferred over calcium chloride, as calcium chloride may cause a metabolic acidosis [13][14]; calcium chloride may be preferred in cases of severe hypocalcemia with poor cardiac function, as liver metabolism is not required for the release of free calcium [6]

Pediatric FDA Approved Indications:
Indicated for the treatment of acute symptomatic hypocalcemia [1].

Administration

•For intravenous use [1].
•Dilute to 10 to 50 mg/mL for bolus and 5.8 to 10 mg/mL for continuous infusion [1].
•Administer bolus slowly [1] over 10 to [8] 30 minutes [6] and do not exceed 100 mg/min [1].
•Avoid intra-arterial infusions of high calcium concentrations. Use caution with the use of an umbilical venous catheter with the tip close to or in the heart [8].
•Administer via secure IV line to avoid calcinosis cutis and tissue necrosis [1].
•Do not administer ceftriaxone and calcium gluconate via Y-site [1].
•If ceftriaxone and calcium gluconate are administered sequentially, then infusions lines should be thoroughly flushed between infusions with a compatible fluid [1].

MEDICATION SAFETY

Contraindications/Precautions

Calcium salts are **contraindicated** in patients with ventricular fibrillation or hypercalcemia (or when calcium levels are above normal). Coadministration of ceftriaxone sodium injection with calcium-containing IV solutions (including continuous calcium-containing infusions such

as parenteral nutrition) is also contraindicated due to the risk of precipitation of ceftriaxone-calcium [15].

Product contains aluminum that may be toxic with prolonged IV administration and in patients with impaired kidney function. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum. Studies showed that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 mcg/kg/day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration. Rapid administration is associated with vasodilation, hypotension, bradycardia, syncope, cardiac arrhythmias, and cardiac arrest[15].

Adverse Effects

Precipitate in the infusion line with crystalline deposits in the lungs and kidneys has been reported in some deceased neonates who were coadministered ceftriaxone IV and calcium-containing fluids, sometimes in the same infusion line. At least one neonatal fatality has been reported following coadministration at different times and with separate infusion lines, though no crystalline deposits were found at autopsy in this neonate. These reports have been confined to neonates [15].

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Amikacin, aminophylline, amiodarone, ampicillin, aztreonam, caffeine citrate, cefazolin, cefepime, chloramphenicol, dobutamine, enalaprilat, epinephrine, famotidine, furosemide, heparin, hydrocortisone, lidocaine, linezolid, micafungin, midazolam, milrinone, netilmicin, nicardipine, penicillin G, phenobarbital, piperacillin-tazobactam, potassium chloride, propofol, remifentanil, tobramycin, and vancomycin.

Terminal Injection Site Incompatibility

Amphotericin B, ceftriaxone, fluconazole, indomethacin, meropenem, methylprednisolone, metoclopramide, and phosphate and magnesium salts when mixed directly.

Monitoring

Therapeutic Laboratory Monitoring
Measure serum calcium every 4 to 6 hours during intermittent infusions and every 1 to 4 hours during continuous infusions. In patients with renal impairment, measure serum calcium every 4 hours [1].
MonitorECG during infusions [1].

Therapeutic Physical Monitoring
Monitor vital signs during infusions [1].

Toxic Laboratory Monitoring
Measure serum calcium every 4 to 6 hours during intermittent infusions and every 1 to 4 hours during continuous infusions. In patients with renal impairment, measure serum calcium every 4 hours [1].
Monitor ECG during infusions [1].
Do not exceed serum ionized calcium concentration 1.5 to 2 times the upper limits of normal when used to reverse calcium channel blocker toxicity [2]

Toxic Physical Monitoring
Monitor vital signs during infusions [1].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of Action: Calcium gluconate increases serum ionized calcium level. Calcium gluconate dissociates into ionized calcium in plasma. Ionized calcium and gluconate are normal constituents of body fluids [1]

Pharmacodynamics
Onset: Immediate [3]

Absorption
Bioavailability (IV): 100% [1]

Metabolism: Does not undergo direct metabolism [1]

Distribution
Extracellular fluid and soft tissues: 1% of total body calcium; the rest (99%) is distributed to the skeleton [1]
Albumin: 40%, serum calcium [1]
Organic and inorganic acid: 8% to 10%, serum calcium [1]

ABOUT

Special Considerations/Preparation

Calcium gluconate 10% injection yields 9.3 mg/mL elemental calcium (0.46 mEq/mL). Osmolarity is 700 mOsm/L. Injectable calcium salts should be stored at room temperature and are stable indefinitely.

DOSING/ADMINISTRATION

Dose

Initial dose: 3 mL/kg/dose (containing 35 mg phospholipids/mL) intratracheally; may be repeated if needed every 12 hours up to a total of 3 doses. For prophylactic therapy in premature infants less than 29 weeks of gestational age at significant risk for respiratory distress syndrome, Infasurf® should be given as soon as possible, preferably within 30 minutes after birth [1]. For rescue therapy, administer as soon as possible, preferably within 2 hours after birth [2].
In the Infasurf® versus Survanta® treatment trial, repeat doses were administered as early as 6 hours after the previous dose for a total of up to 4 doses if the infant was still intubated and required at least 30% inspired oxygen to maintain a PaO_2 of 80 torr or less [1].

Uses

Respiratory distress syndrome (RDS): Routine continuous positive airway pressure (CPAP) is considered superior to prophylactic surfactant therapy. It is strongly recommended that CPAP immediately after birth with subsequent selective surfactant administration be considered as an alternative to routine intubation with prophylactic or early surfactant administration in preterm infants. Severe RDS in preterm infants born younger than 30 weeks gestation who need mechanical ventilation should be administered surfactant after initial stabilization. Consider the use of rescue surfactant for infants with hypoxic respiratory failure attributable to secondary surfactant deficiency, such as meconium aspiration syndrome or sepsis/pneumonia[2]. Animal-derived surfactants (beractant, calfactant, and poractant alfa) had comparable outcomes for air leak syndromes, death, and bronchopulmonary dysplasia in a retrospective study (n=51,282; median birth weight of 1435 g; median gestation age of 30 weeks (27 to 33 weeks)) [4]. In a prospective randomized trial, the animal-derived surfactants all improved FiO2 need, PaO2 values, chest x-ray findings, and lung ultrasonography (LUS) scores (N=62, gestational age range 24 to 34 weeks, birthweight range 560 to 2500 g). However, the results were significantly better with poractant alfa and beractant compared with calfactant. The FiO2 values at 24 hours post-surfactant for poractant alfa, beractant, and calfactant were 36.8%, 33.6%, and 53.1%, respectively. The PaO2 values at 24 hours post-surfactant for poractant alfa, beractant, and calfactant were 64.7, 66.3, and 61.3 mmHg, respectively. The LUS scores at 24 hours post-surfactant for poractant alfa, beractant, and calfactant were 3.8, 4.3, and 6.9, respectively. Significantly more calfactant-treated patients required repeat dosing. Mechanical ventilation duration and hospital length of stay were similar between all 3 groups [5].
Late Administration: Calfactant administered at 7 to 14 days of age in infants (28 weeks of gestational age or younger) who required mechanical ventilation and were receiving inhaled nitric oxide did not improve survival without bronchopulmonary dysplasia (BPD) at 36 weeks' or 40 weeks' postmenstrual age or improve the severity of BPD, in a randomized,

masked, multicenter trial (n=511). Infants were randomized to either calfactant every 24 to 72 hours up to 5 doses, if the infants still required intubation, or sham. Due to unlikely benefit the trial was terminated early [6]. At 1-year corrected age follow-up (n=450), home respiratory support was reduced with late surfactant compared with inhaled nitric oxide alone. However, no improvement was noted on composite outcome of pulmonary morbidity (PM) (measured by use of medications, hospitalization, and home respiratory support) or persistent PM [7].

Neonatal FDA-Approved Indications

Infasurf® is indicated for the prevention of respiratory distress syndrome (RDS) in premature infants less than 29 weeks of gestational age at significant risk for RDS. Treatment should be given as soon as possible, preferably within 30 minutes after birth [1][8][9].

Infasurf® is indicated for infants less than 72 hours of age with RDS (confirmed by clinical and radiological findings) and requiring endotracheal intubation [1][8][10].

Administration

For intratracheal administration only [3].

Warming of suspension is not necessary [3]

Calfactant intratracheal suspension may be administered by either of the following 2 methods [3]:

- 1) Administration by instilling the suspension through a side-port adapter into the endotracheal tube. Two attendants are needed to facilitate dosing; one to instill the calfactant, the other to monitor the patient and assist in positioning. The dose (3 mL/kg) should be administered in 2 aliquots of 1.5 mL/kg each. After each aliquot is instilled, the neonate should be positioned with either the right or the left side dependent. Administration is made while ventilation is continued over 20 to 30 breaths for each aliquot, with small bursts timed only during the inspiratory cycles. A pause followed by evaluation of the respiratory status and repositioning should separate the two aliquots.
- 2) Administration by instilling the suspension through a 5 French feeding tube inserted into the endotracheal tube. The total dose is instilled in 4 equal aliquots with the catheter removed between each instillation and mechanical ventilation resumed for 0.5 to 2 minutes. For even distribution of calfactant, each of the aliquots should be administered with the neonate in 1 of 4 positions; prone, supine, right, and left lateral.

MEDICATION SAFETY

Contraindications/Precautions

Transient episodes of reflux of surfactant into the endotracheal tube, cyanosis, bradycardia, and airway obstruction have been reported during administration. A higher rate of intraventricular hemorrhage and periventricular leukomalacia was observed in Infasurf®-

treated infants compared with Exosurf®-treated infants in clinical trials [1].

Adverse Effects

Most common adverse reactions observed in clinical trials were cyanosis (65%), airway obstruction (39%), bradycardia (34%), reflux of surfactant into the endotracheal tube (21%), requirement for manual ventilation (16%), and reintubation (3%). Reactions were usually transient and not associated with severe complications or mortality [1].

Monitoring

Monitor closely for appropriate oxygen therapy and ventilatory support [1].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Pulmonary lung surfactants are essential for effective ventilation by modifying alveolar surface tension thereby stabilizing the alveoli. Infasurf® is a sterile, non-pyrogenic natural surfactant extracted from calf lungs containing phospholipids, neutral lipids, fatty acids, and surfactant-associated proteins B and C. Preservative free. Each mL of Infasurf® contains 35 mg of total phospholipids (26 mg of phosphatidylcholine of which 16 mg is disaturated phosphatidylcholine) and 0.65 mg of proteins including 0.26 mg of SP-B [1].

ABOUT

Special Considerations/Preparation

Available in 3-mL and 6-mL single-use vials. Refrigerate at 2 to 8 degrees C (36 to 46 degrees F) and protect from light. **The 3 mL vial must be stored upright.** Inspect Infasurf® for discoloration; normal color is off-white, and visible flecks and foaming at the surface are normal. Suspension settles during storage; gently swirl vial in order to uniformly suspend. **Do not shake.** Used vials with residual drug should be discarded. Unopened vials that have been warmed to room temperature one time may be refrigerated within 24 hours and stored for future use. Should not be warmed and returned to the refrigerator more than once [1].

Captopril

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Initial dose: 0.01 mg/kg/dose orally every 12 hours. Incrementally increase dose [1][2]. Adjust dose and interval based on response.
Dosage: 0.1 to 0.4 mg/kg/dose orally every 6 hours [2][3] to 24 hours [3] has been suggested for hypertension. In neonates with heart failure, 0.4 to 1.6 mg/kg/day orally divided every 8 hours was recommended [4]; based on a retrospective study for congenital heart disease 1 to **maximum 1.5 mg/kg/day** orally divided every 8 hours was suggested [5].
A significant decrease in creatinine clearance in preterm and term neonates with cardiovascular disease warrants extreme care in term neonates treated with captopril and questions the use of captopril in preterm neonates in a retrospective review (n=206) [6].

Uses

Heart failure: Afterload reduction in patients with congestive heart failure.
Hypertension: Treatment of moderate to severe hypertension.

Administration

Administer 1 hour before feeding; food decreases absorption.

MEDICATION SAFETY

Contraindications/Precautions

The use of captopril is contraindicated in patients with bilateral renovascular disease or with unilateral renal artery stenosis in a solitary kidney, as the loss of adequate renal perfusion could precipitate acute renal failure.

Adverse Effects

Neonates are more sensitive to the effects of captopril than are older infants and children. Significant decreases in cerebral and renal blood flow have occurred in premature infants with chronic hypertension who received higher doses (0.15 to 0.30 mg/kg per dose) than those recommended above. These episodes occurred unpredictably during chronic therapy, and some were associated with neurologic (seizures, apnea, lethargy) and renal (oliguria) complications. Hyperkalemia occurs primarily in patients receiving potassium-sparing diuretics or potassium supplements [7].
The CrCl significantly decreased in preterm and term neonates with cardiovascular disease after initiation of ACEIs (captopril or enalapril) in a retrospective review (n=206). The body surface area was less than 0.33 m^2 for all neonates [6].

Monitoring

- Frequent assessment of blood pressure, particularly after the first dose.
- Periodic assessment of renal function
- Periodic measurement of serum potassium.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action: Captopril is an angiotensin-converting enzyme (ACE) inhibitor that blocks the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor. It thereby decreases plasma and tissue concentrations of angiotensin II and aldosterone, and increases plasma and tissue renin activity. Captopril also prevents the breakdown of bradykinin, a potent vasodilator. Vascular resistance is reduced without reflex tachycardia. Beneficial effects are thought to be caused by a combination of afterload reduction and long-term inhibition of salt and water retention.
Bioavailability is good in neonates, although food will decrease absorption.
Onset of action is 15 minutes after a dose, with peak effects seen in 30 to 90 minutes.
Duration of action is usually 2 to 6 hours, but may be significantly longer (greater than 24 hours).

ABOUT

Special Considerations/Preparation

Available in 12.5-mg, 25-mg, 50-mg, and 100-mg tablets.

Extemporaneous Oral Compounds

Captopril 1 mg/mL oral solution was stable for 56 days at 4 degrees C and *28 days at 22 degrees C*. Two captopril 50-mg tablets were dissolved in 50 mL of water in a graduate. One *ascorbic acid 500-mg tablet* was added and allowed to dissolve. Sufficient distilled water was added for a final volume of 100 mL. Shake well. Do not filter [8].

Captopril 1 mg/mL oral solution was stable for 56 days at 4 degrees C and 14 days at *22 degrees C*. Two captopril 50-mg tablets were dissolved in 50 mL of water in a graduate. *Sodium ascorbate injection* 500 mg was added and mixed well. Sufficient distilled water was added for a final volume of 100 mL. Shake well. Do not filter [8].

Captopril 0.03 mg/mL oral suspension was stable for 14 days at room temperature or 56 days when refrigerated. Captopril 6.25 mg (one-half of a scored 12.5-mg tablet) was dissolved in 10 mL of sterile water, 1000 mg of sodium ascorbate for injection (4 mL of 250-mg/mL solution) was added to decrease oxidation, then sufficient water was added to make a final volume of 200 mL. The final concentration was 0.03 mg/mL captopril and 5 mg/mL sodium ascorbate. Some undissolved excipients remained visible [9].

Aqueous captopril solutions have been reported to degrade rapidly, and stability in different solutions is highly variable and dependent on many factors (pH, type of vehicle, drug concentration, addition of preservative). There have been conflicting results in various studies over the years. The data below represents some of the studies of various extemporaneously prepared captopril oral solutions [10][11][9].
Captopril 1 mg/mL oral solution made with tablets and undiluted syrup was stable for 30 days refrigerated (5 degrees C). In this study, different formulations of captopril solutions were made using either tablets or powder with different vehicles used (sterile water, syrup, methylcellulose); edetate disodium was added to some of the formulations. Better stability was noted when captopril tablets were used compared with powder, with undiluted versus diluted syrup as the vehicle, and when edetate disodium was added as the preservative [11].
To overcome potential stability problems, powder papers and compounded capsules have been utilized to extemporaneously prepare captopril solutions just prior to administration [12][13].

Carglumic Acid

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Critical Dosing Notes:
• Initiate carglumic acid treatment as soon as the diagnosis of N-acetylglutamate synthase (NAGS) deficiency is suspected, which may be as soon as at birth, and managed by a physician and medical team experienced in metabolic disorders [1].
• Initiate treatment of acute hyperammonemia in patients with a suspected or confirmed diagnosis of propionic acidemia (PA) or methylmalonic acidemia (MMA) [1].

Acute Hyperammonemia due to N-acetylglutamate synthase (NAGS) deficiency; Adjunct
Note: Titrate dosage to maintain the plasma ammonia level within the normal range for patient age and clinical condition[1]
Usual dosage: 100 to 250 mg/kg/day orally or via NG tube divided into 2 to 4 doses per day (rounded to the nearest 100 mg) [1][2]
Concomitant medications: During acute hyperammonemic episodes, administer with other ammonia-lowering therapies (eg, alternate pathway medications, hemodialysis and protein restriction) [1]

Chronic Hyperammonemia due to N-acetylglutamate synthase (NAGS) deficiency; Maintenance
Note: Titrate dosage to maintain the plasma ammonia level within the normal range for patient age and clinical condition[1]
Usual dosage: 10 to 100 mg/kg/day orally or via NG tube divided into 2 to 4 doses (rounded to the nearest 100 mg) [1]
Concomitant medications: Use of other ammonia lowering therapies and protein restriction may be needed [1]

Acute Hyperammonemia due to Propionic Acidemia (PA) or Methylmalonic Acidemia (MMA); Adjunct
Usual dose, 15 kg or less: 150 mg/kg/day orally or via NG tube divided into 2 equal doses; rounding up to next multiple of 50 mg. Administer doses 12 hours apart until ammonia level is less than 50 micromol/L and for a maximum duration of 7 days [1]
Treatment duration: Continue until ammonia level is less than 50 mcmol/L and for a maximum duration of 7 days [1]
Concomitant medications: Give with other ammonia lowering therapies (eg, IV glucose, insulin, L-carnitine, protein restriction, and dialysis) [1].

Uses

Treatment of hyperammonemia due to various metabolic disorders [2][3]. Based upon use in newborns from case reports, carglumic acid, when administered in addition to standard therapy, acutely reduces plasma ammonia levels in patients with branched-chain organic acidemias, such as methylmalonic aciduria (MMA), propionic aciduria (PA), and isovaleric acidemia (IVA) . In these metabolic disorders, synthesis of N-acetylglutamate is inhibited due to the build up of the respective branched-chain organic acid; once standard therapy has corrected the acidemia, hyperammonemia is also resolved [4]. Doses used in these cases ranged from 70 to 200 mg/kg/day, administered as a single dose [4] or over a 48-hour period [3].

FDA Approved Indications

Indicated as adjunctive therapy for the treatment of acute hyperammonemia due to deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS) from the time of birth. Also indicated as maintenance therapy for chronic hyperammonemia due to NAGS deficiency [1].

Indicated in pediatric patients as adjunctive therapy to standard of care for the treatment of acute hyperammonemia due to propionic acidemia (PA) or methylmalonic acidemia (MMA) [1]

Administration

General Information

- Disperse tablets in water, do not swallow whole or crushed [1]
- Tablets do not dissolve completely in water, and undissolved particles of the tablet may remain in the mixing container [1]
- Administer immediately before meals or feedings [1]
- Do not mix in other foods or liquids other than water [1]

Oral

- Swallow mixture immediately; pieces of tablet(s) may remain in cup; add additional water and swallow mixture immediately; repeat as needed until no pieces of the tablet are left in the cup [1]
- If using an oral syringe, draw up mixture after mixing and administer immediately; pieces may remain in oral syringe; refill oral syringe with a minimum of 1 to 2 mL of water and administer immediately; flush again, as needed until no pieces of the tablet are left [1]

NG Tube

- Draw up mixture into a catheter-tip syringe; administer immediately via NG or G-tube [1]
- Pieces of tablet(s) may remain in catheter-tip syringe or feeding tube; flush immediately with 1 to 2 mL of water; repeat as needed until no pieces of the tablet are left in the syringe [1]

MEDICATION SAFETY

Contraindications/Precautions

Contraindications
Specific contraindications have not been determined [1]

Precautions
Specific precautions have not been determined [1]

Adverse Effects

Common, N-acetylglutamate synthase deficiency, 13% or greater: Abdominal pain (17%), anemia (13%), diarrhea (13%), ear infection (13%), headache (13%), infection (13%), nasopharyngitis (13%), pyrexia (17%), tonsillitis (17%), and vomiting (17%) [1][2].
Common, propionic acidemia and methylmalonic acidemia, 5% or greater: Neutropenia (14%), anemia (12%), vomiting (7%), electrolyte imbalance (7%), decreased appetite (5%), hypoglycemia (5%), lethargy/stupor (5%), encephalopathy (5%), pancreatitis/increased lipase (5%) [1]

Monitoring

Therapeutic and Toxic Laboratory Monitoring
Monitor plasma ammonia levels and clinical response [1].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action: Carglumic acid is a synthetic analogue of N-acetylglutamate (NAG), a product of N-acetylglutamate synthase (NAGS). NAG is an essential activator of carbamoyl phosphate synthetase 1 (CPS 1), which is the first enzyme in the urea cycle. Carglumic acid acts as a replacement for NAG in patients with NAGS deficiency, thereby activating CPS 1 [1].

Pharmacodynamics
Pharmacodynamics onset, initial response
- **Ammonia level reduction:** 24 hours [1]

Therapeutic Drug Concentrations
AUC
- **IV, 8 mg/kg, healthy volunteers:** 24501 nanograms (ng) x hr/mL [1]
- **Oral, 100 mg/kg, healthy volunteers:** 31426 nanograms (ng) x hr/mL [1]

Peak concentration

• **IV, 8 mg/kg, healthy volunteers:** 8613 nanograms (ng)/mL [1]
• **Oral, 100 mg/kg, healthy volunteers:** 3284 nanograms (ng)/mL [1]

Time to peak concentration
• **IV, 8 mg/kg, healthy volunteers:** 2 hours [1]
• **Oral, 100 mg/kg, healthy volunteers:** 3 hours [1]

Absorption

Bioavailability
• **Oral, 100 mg/kg, healthy volunteers:** Approximately 10% [1]

Distribution

Kinetics
• **IV, 8 mg/kg, healthy volunteers:** 15 L/kg [1]

Metabolism

Sites and kinetics: Intestinal bacteria [1]

Metabolic enzymes and transporters
• **Substrate of:** Human OAT1 transporter [1]

Excretion

Renal excretion
• **Oral, 100 mg/kg, healthy volunteers:** 9% (unchanged) [1]

Feces
• **Oral, 100 mg/kg, healthy volunteers:** 60% (unchanged) [1]

Total body
• **IV, 8 mg/kg, healthy volunteers:** 0.34 L/hr/kg [1]

Elimination Half-Life
• **IV, 8 mg/kg, healthy volunteers:** 31 hours [1]
• **Oral, 100 mg/kg, healthy volunteers:** 25 hours [1]

ABOUT

Special Considerations/Preparation

Availability: 200 mg tablet for oral suspension, functionally scored with 3 lines for splitting into 4 equal portions [1]
Storage: Store in the original unopened container between 2 and 8 degrees C (36 and 46 degrees F) [1].
After opening, do not refrigerate and store at a room temperature between 15 and 30 degrees (59 and 86 degrees F); protect from moisture [1].
Discard one month after first opening [1].

Caspofungin

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Aspergillus or Candida Infection, Suspected or Documented:
25 mg/m^2/dose IV every 24 hours [1]. This dose has not been evaluated in clinical studies. Duration of therapy for candidemia, without metastatic complications, is 2 weeks after documented clearance of *Candida* from the bloodstream and resolution of symptoms [2].

Candidiasis - HIV Infection
Esophageal disease:
• **Less than 3 months (alternate therapy):** 25 mg/m^2 IV once daily for at least 3 weeks and for at least 2 weeks following resolution of symptoms [3]
Invasive disease:
• **Critically-ill, less than 3 months:** 25 mg/m^2 IV once daily. Duration of treatment is based on presence of deep-tissue foci and clinical response; in patients with candidemia, treat until 2 weeks after a positive blood culture [3]

Uses

Aspergillus or Candida Infection:
Treatment of patients with refractory Candidemia, intra-abdominal abscesses, peritonitis and pleural space infections, and those patients intolerant of amphotericin B. Treatment of invasive Aspergillosis in patients who are refractory to or intolerant of other therapies.

There are case reports, but not controlled clinical trials, treating endocarditis, osteomyelitis, and meningitis due to *Candida*.

Neonatal Candidiasis, Including CNS Infection[2]
Invasive candidiasis, candidemia, or very low-birth weight infants with asymptomatic candiduria .

- Amphotericin B deoxycholate is recommended.
- Fluconazole IV or oral is an alternative for those who have not been receiving prophylaxis with fluconazole.
- Lipid formulation amphotericin B agent is an alternative; however, use with caution, especially in the presence of urinary tract involvement.
- Echinocandins (caspofungin, anidulafungin, or micafungin) should be limited to salvage therapy or scenarios of resistance or toxicity to amphotericin B deoxycholate or fluconazole.

Central nervous system infections

- Amphotericin B deoxycholate is recommended.
- Liposomal amphotericin B agent is an alternative.
- Salvage therapy with flucytosine may be added in those patients who have not responded to initial therapy.
- Fluconazole may be used as step-down therapy for fluconazole-susceptible isolates in those patients who respond to initial therapy.

Neonatal intensive care unit (with greater than 10% rate of invasive candidiasis)

- Prophylaxis with IV or oral fluconazole for 6 weeks is recommended for neonates with birth weights of less than 1000 g
- Prophylaxis with oral nystatin is an alternative in neonates with birth weights of less than 1500 g when fluconazole is unavailable or fluconazole resistance is present

HIV Infection - Candidiasis: Caspofungin is recommended as a first-line agent to treat invasive candidiasis in critically-ill patients with HIV co-infection [3].

Comparison to Amphotericin B: There was no difference in clinical response between echinocandins and amphotericin B (OR 1.38; 95% CI, 0.68 to 2.8) for the treatment of suspected or confirmed invasive candidiasis in a meta-analysis (n=5; 354 neonates and children). Antifungals included were micafungin, caspofungin, amphotericin B deoxycholate, and liposomal amphotericin B. Subanalysis demonstrated no difference in other comparisons including mycological response, mortality, recurrence of candida infection, type of echinocandin, different risk groups (high-risk, low-risk, or neutropenic groups), and type of use (targeted or empirical). Discontinuation due to adverse effects were higher with amphotericin B than the echinocandins (OR 0.3; 95% CI, 0.12 to 0.76) [6].

Pediatric FDA Approved Indications

The following indications are FDA approved for pediatric patients 3 months and older [7]:

- Empirical therapy for presumed fungal infections in febrile, neutropenic patients.
- Treatment of candidemia and the following *Candida* infections: intraabdominal abscesses, peritonitis and pleural space infections.
- Treatment of esophageal candidiasis.
- Treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies.

Administration

Administer by slow IV infusion over approximately 1 hour at a **concentration not to exceed 0.5 mg/mL.**[4] The recommended concentration is 0.5 mg/mL [5]. **Do not dilute in dextrose-containing solutions**.

MEDICATION SAFETY

Contraindications/Precautions

Concomitant Use: Increased risk of hepatotoxicity when used with cyclosporine [7].
Dermatologic: Stevens-Johnson syndrome and toxic epiderma necrolysis, sometimes fatal, have been reported; discontinue at first sign or symptom [8]
Hepatic: Hepatic abnormalities, including abnormal liver function tests and hepatic failure, have been reported; monitoring recommended [7].
Hepatic: Dose adjustment may be required for hepatic impairment [7].
Immunologic: Anaphylaxis and other hypersensitivity reactions have been reported; discontinue use if occurs [8].
Immunologic: Histamine-mediated adverse reactions (eg, rash, facial swelling, angioedema, pruritus, sensation of warmth, bronchospasm) have been reported; discontinuation may be necessary [8].

Adverse Effects

Adverse effects reported in neonates (small number of patients): thrombophlebitis, hypercalcemia, hypokalemia, elevated liver enzymes, and isolated direct hyperbilirubinemia. In pediatric studies, the primary adverse effects were fever, hypokalemia, diarrhea, increased liver enzymes, rash, hypotension and chills.

Solution Compatibility

NS, ½ NS, ¼ NS, LR.

Solution Incompatibility

All solutions containing dextrose.

Terminal Injection Site Compatibility

Azithromycin, aztreonam, dobutamine, dopamine, famotidine, fluconazole, insulin, linezolid, meropenem, metronidazole, morphine, potassium chloride, and vancomycin.

Terminal Injection Site Incompatibility

Acyclovir, cefazolin, ceftriaxone, clindamycin, furosemide, heparin, and piperacillin/tazobactam.

Monitoring

Assess IV site for signs of irritation. Periodic measurement of serum potassium, calcium, and hepatic transaminases.
For candidemia, monitor blood cultures daily or every other day until *Candida* is cleared [2].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Caspofungin is the first of a new class of antifungal agents (echinocandins) that inhibit the synthesis of β-(1,3)-D-glucan, an integral component of the fungal cell wall. It is fungicidal against *Candida* species, but fungistatic against *Aspergillus*. The echinocandins are excreted primarily by the liver, presumably metabolized through an O-methyltransferase. They are not metabolized through the CYP enzyme system and therefore have significantly fewer drug-drug interactions than the azoles. Dexamethasone, phenytoin, carbamazepine, nevirapine, and rifampin all induce caspofungin drug clearance, lowering serum concentrations.

In a pharmacokinetic study in infants less than 3 months (n=18) with esophageal/oropharyngeal candidiasis or invasive candidiasis, a dose of 25 mg/m^2 appeared to provide similar drug exposure compared with adults receiving 50 mg/dose. The majority of infants were born premature (approximately 70%) and 12 of 18 infants were 4 weeks postnatal age or younger [9].

ABOUT

Special Considerations/Preparation

Cancidas® is supplied as a white to off-white powder cake in single-use vials, containing either 50 or 70 mg. To prepare the 50-mg (5 mg/mL) or 70-mg (7 mg/mL) Cancidas® vial: 1) Equilibrate the refrigerated vial to room temperature. 2) Aseptically add 10.8 mL Normal Saline or Sterile Water for Injection to the vial. The powder cake will dissolve completely with gentle mixing. This reconstituted solution can be stored at room temperature for up to one hour. Visually inspect the reconstituted solution for particulate matter or discoloration. Do not

use if the solution is cloudy or has precipitated. Single-use vials: discard remaining unused solution. 3) Remove desired volume of drug based on calculated dose and further dilute in compatible solution (NS, ½ NS, ¼ NS, LR) to a final concentration not to exceed 0.5 mg/mL. The infusion solution can be stored for up to 24 hours at room temperature or up to 48 hours refrigerated. **Do not use diluents containing dextrose**.

DOSING/ADMINISTRATION

Dose

25 mg/kg/dose IV or IM.

Antibiotic Dosing Chart:
Renal function and drug elimination are most strongly correlated with Postmenstrual Age (PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.

Dosing Interval Chart		
PMA (weeks)	**PostNatal (days)**	**Interval (hours)**
≤29	0 to 28 >28	12 8
30 to 36	0 to 14 >14	12 8
37 to 44	0 to 7 >7	12 8
≥45	ALL	6

Uses

Use in neonates is generally limited to perioperative infection prophylaxis and treatment of urinary tract and soft tissue infections caused by susceptible organisms, e.g. penicillin-resistant *Staph. aureus*, *Klebsiella*, and *Proteus.*

Infective endocarditis: The following recommendations are based on a consensus of experts [3]. The full pediatric guidelines can be found here: https://doi.org/10.1161/CIR.0000000000000298

Organism Directed Therapy		
Organism	First-Choice	Alternative Choice
Streptococci		
Highly susceptible to penicillin G (MBC 0.1 mcg/mL or less); includes most viridans	Penicillin G or CefTRIAXone	Vancomycin or First-generation cephalosporin or CefTRIAXone

streptococci, groups A, B, C, G nonenterococcal, group D streptococci (S bovis, S equinus)		
Relatively resistant to penicillin (MBC 0.2 mcg/mL or more); less-susceptible viridans streptococci or enterococci	Penicillin G or Ampicillin + Gentamicin (for first 2 weeks, or entire course for enterococci)	Vancomycin + Gentamicin for enterococci Ampicillin + CefTRIAXone (for aminoglycoside (AMG)-resistant enterococci or AMG-intolerant patient) CefTRIAXone + gentamicin (not for enterococcal endocarditis)
Resistant to penicillin	Consult an infectious disease specialist.	---
Staphylococci (S aureus or coagulase-negative staphylococci) †		
Penicillin G susceptible (1 mcg/mL or less) (rare)	Penicillin G	Oxacillin or Nafcillin or First-generation cephalosporin or Vancomycin
Penicillin G resistant (0.1 mcg/mL)	Oxacillin or Nafcillin with or without Gentamicin	Vancomycin (for those highly allergic to beta-lactam antibiotics) or First-generation cephalosporin
Oxacillin (MRSA) resistant (4 mcg/mL)	Vancomycin	Daptomycin for right-sided endocarditis, maybe for left-sided
Vancomycin resistant or intolerant	Daptomycin	Unknown

	†When prosthetic material present add riFAMpin + gentamicin (for first 2 weeks) for all staphylococci	
Gram-negative enteric bacilli	CefTAZidime or Cefepime or Cefotaxime or CefTRIAXone Plus gentamicin (or tobramycin or amikacin, depending on susceptibility)	Broad-spectrum penicillin Plus gentamicin (or tobramycin or amikacin)
HACEK group	CefTRIAXone or Cefotaxime or Ampicillin-sulbactam	Ampicillin (when susceptible) Plus aminoglycoside
KEY: AMG = aminoglycosides; HACEK = Haemophilus species, Aggregatibacter species, Cardiobacterium hominis, Eikenella corrodens, and Kingella species; MBC = minimum bactericidal concentration, MRSA = methicillin-resistant Staphylococcus aureus (includes resistance to oxacillin, nafcillin, and cephalosporins)		
Baltimore, 2015		

Sepsis, Prophylaxis; Catheter Removal: Reductions (11% vs 0%; p=0.021) in culture-confirmed sepsis were demonstrated in a prospective randomized controlled study in 88 preterm infants administered cefazolin 1 hour prior to and 12 hours after removal of a PICC line compared with no antibiotic use[4]. However, this study was criticized for methodology shortcomings that limit its applicability [5]. Sepsis rates were 10.3% with removal of a PICC without antibiotics 48 hours prior to removal compared with 1.5% (p=0.002) in neonates on cefazolin/gentamicin at the time of removal of the PICC in a retrospective study (n=345) [6].

Administration

May be given by IV direct (bolus) injection, IV infusion, or IM injection [1][2].
For IV bolus injection, inject slowly over 3 to 5 minutes at a concentration of 100 mg/mL. For IV intermittent or continuous infusion, dilute reconstituted solution to a concentration of 5 to 20 mg/mL [1][2].
For IM injection, use a concentration of 225 mg/mL. **Maximum 330 mg/mL**[1][2].

MEDICATION SAFETY

Adverse Effects

Adverse effects are rare, but include phlebitis and eosinophilia.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Acyclovir, alprostadil, amikacin, aztreonam, calcium gluconate, clindamycin, enalaprilat, esmolol, famotidine, fluconazole, heparin, insulin, lidocaine, linezolid, magnesium sulfate, midazolam, milrinone, morphine, metronidazole, multivitamins, nicardipine, pancuronium bromide, propofol, prostaglandin E_1, ranitidine, remifentanil, and vecuronium.

Terminal Injection Site Incompatibility

Amiodarone, caspofungin, cimetidine, and vancomycin.

Monitoring

Serum concentrations are not routinely monitored.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

First generation cephalosporin that is bactericidal against many gram-positive and a few gram-negative organisms. Inactivated by β-lactamase producing organisms. Poor CNS penetration. Renally excreted as unchanged drug. Half-life in neonates is 3 to 5 hours.

ABOUT

Special Considerations/Preparation

Availability: Powder for injection in 500-mg and 1000-mg vials.
Reconstitution: 2 mL of sterile water for injection in 500 mg vial for 225 mg/mL concentration and 2.5 mL of sterile water for injection in 1000 mg vial for a 330 mg/mL concentration. Reconstituted solution stable for 24 hours at room temperature or 10 days in refrigerator [1].
Dilutions: Further dilute reconstituted solution in 5 mL of sterile for injection for a bolus injection or dilute in 50 to 100 mL of a compatible solution for intermittent or continuous infusion. Solution stable for 24 hours at room temperature or 10 days in refrigerator [1].

Cefepime

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Term and preterm infants greater than 28 days of age: 50 mg/kg/dose IV every 12 hours.

Term and preterm infants 28 days of age and younger: 30 mg/kg/dose IV every 12 hours.

Meningitis and severe infections due to Pseudomonas aeruginosa or Enterobacter spp: 50 mg/kg/dose IV every 12 hours.

Uses

Treatment of serious infections caused by susceptible gram-negative organisms (eg, *E coli, H influenzae, Enterobacter, Klebsiella,Morganella*, *Neisseria, Serratia,* and *Proteus* species), especially *Pseudomonas aeruginosa* that are resistant to 3rd generation cephalosporins. Treatment of serious infections caused by susceptible Gram-positive organisms (eg, *Strep pneumoniae, Strep. pyogenes, Strep. agalactiae, and Staph. aureus*).

A positive clinical response was observed in 26 of the 32 (81.3%) evaluable neonates treated with cefepime (mean dose 36 mg/kg/dose IV every 12 hours) in a retrospective, single-center study (n=74; mean postmenstrual age at initiation, 33 weeks). Concomitant antibiotics were used during all courses; most common infections were late-onset sepsis (42%), early-onset sepsis (17.6%), and multiple indications (16.2%) [3].

Infective endocarditis: The following recommendations are based on a consensus of experts [4]. The full pediatric guidelines can be found here: https://doi.org/10.1161/CIR.0000000000000298

<table>
<tr><td colspan="3">Initial Empirical Therapy or Culture-Negative Endocarditis*</td></tr>
<tr><td>Unknown Organism</td><td>First-Choice</td><td>Alternative Choice</td></tr>
<tr><td>Native valve (community acquired)</td><td rowspan="2">Ampicillin/sulbactam + gentamicin with or without vancomycin
For prosthetic valve involvement, add rifAMPin</td><td rowspan="2">Vancomycin + gentamicin</td></tr>
<tr><td>"Late" prosthetic valve infection (more than 1</td></tr>
</table>

year after surgery)		
Nosocomial endocarditis associated with vascular cannulae	Vancomycin + gentamicin (with or without rifAMPin if prosthetic material present) + cefepime or cefTAZidime	Unknown
"Early" prosthetic valve endocarditis (1 year or less after surgery)		
* Culture-negative endocarditis (CNE): generally, attempt to culture the infecting organism for at least 48 hours. Severely ill children need immediate treatment. Consider infectious disease consultation for CNE		
Baltimore, 2015		

Organism Directed Therapy		
Organism	First-Choice	Alternative Choice
Streptococci		
Highly susceptible to penicillin G (MBC 0.1 mcg/mL or less); includes most viridans streptococci, groups A, B, C, G nonenterococcal, group D streptococci (S bovis, S equinus)	Penicillin G or CefTRIAXone	Vancomycin or First-generation cephalosporin or CefTRIAXone
Relatively resistant to penicillin (MBC 0.2 mcg/mL or more); less-susceptible viridans streptococci or enterococci	Penicillin G or Ampicillin + Gentamicin (for first 2 weeks, or entire course for enterococci)	Vancomycin + Gentamicin for enterococci Ampicillin + CefTRIAXone (for aminoglycoside (AMG)-resistant enterococci or AMG-intolerant patient) CefTRIAXone + gentamicin (not for enterococcal endocarditis)

Resistant to penicillin	Consult an infectious disease specialist.	---
Staphylococci (S aureus or coagulase-negative staphylococci) †		
Penicillin G susceptible (1 mcg/mL or less) (rare)	Penicillin G	Oxacillin or Nafcillin or First-generation cephalosporin or Vancomycin
Penicillin G resistant (0.1 mcg/mL)	Oxacillin or Nafcillin with or without Gentamicin	Vancomycin (for those highly allergic to beta-lactam antibiotics) or First-generation cephalosporin
Oxacillin (MRSA) resistant (4 mcg/mL)	Vancomycin	Daptomycin for right-sided endocarditis, maybe for left-sided
Vancomycin resistant or intolerant	Daptomycin	Unknown
	†When prosthetic material present add riFAMpin + gentamicin (for first 2 weeks) for all staphylococci	
Gram-negative enteric bacilli	CefTAZidime or Cefepime or Cefotaxime or CefTRIAXone Plus gentamicin (or tobramycin or amikacin, depending on susceptibility)	Broad-spectrum penicillin Plus gentamicin (or tobramycin or amikacin)
HACEK group	CefTRIAXone or Cefotaxime or Ampicillin-sulbactam	Ampicillin (when susceptible) Plus aminoglycoside

KEY: AMG = aminoglycosides; HACEK = Haemophilus species, Aggregatibacter species, Cardiobacterium hominis, Eikenella corrodens, and Kingella species; MBC = minimum bactericidal concentration, MRSA = methicillin-resistant Staphylococcus aureus (includes resistance to oxacillin, nafcillin, and cephalosporins)
Baltimore, 2015

Administration

Give as an IV infusion in a compatible solution over 30 minutes at a concentration of 1 to [1] 100 mg/mL. A large healthcare system selected 40 mg/mL and 100 mg/mL (IV push) as standard concentrations for cefepime [2].
May be given by IM injection at a concentration of 280 mg/mL [1]. To reduce pain at IM injection site, cefepime may be mixed with 1% lidocaine without epinephrine.

MEDICATION SAFETY

Adverse Effects

Safety has been documented to be the same as commonly used second- and third-generation cephalosporins. Reported adverse effects are uncommon, but include rash, diarrhea, elevated hepatic transaminases, eosinophilia, and positive Coomb's test.

In a retrospective, single-center study of 74 neonates (mean postmenstrual age at initiation was 33 weeks) treated with cefepime (mean dose 36 mg/kg/dose IV every 12 hours), acute kidney injury (16.2%), hypophosphatemia (12.2%), seizures (0.03%), and hyponatremia (0.01%) were reported. Concomitant nephrotoxic agents (i.e., vancomycin and gentamicin) were used in all neonates [3].

Solution Compatibility

D_5W, $D_{10}W$, D_5LR, D_5NS, and NS.

Terminal Injection Site Compatibility

Amikacin, ampicillin, aztreonam, bumetanide, calcium gluconate, clindamycin, dexamethasone, fluconazole, furosemide, gentamicin, heparin, hydrocortisone succinate, imipenem/cilastatin, lorazepam, methylprednisolone, metronidazole, milrinone, piperacillin-tazobactam, potassium chloride, ranitidine, remifentanil, sodium bicarbonate, ticarcillin/clavulanate, trimethoprim/sulfamethoxazole, and zidovudine.

Terminal Injection Site Incompatibility

Acyclovir, aminophylline, amphotericin B, cimetidine, diazepam, dobutamine, dopamine, enalaprilat, erythromycin lactobionate, famotidine, ganciclovir, magnesium sulfate, metoclopramide, midazolam, morphine, nicardipine, phenytoin, tobramycin, and vancomycin.

Monitoring

Measuring serum concentration is not usually necessary.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Cefepime is a fourth-generation cephalosporin with treatment efficacy equivalent to third-generation cephalosporins. Potential advantages include: more rapid penetration through the cell wall of Gram-negative pathogens; enhanced stability to hydrolysis by β-lactamases; and enhanced affinity for penicillin-binding proteins. The drug distributes widely in body tissues and fluids (i.e. CSF, bile, bronchial secretions, lung tissue, ascitic fluid, middle ear). Protein binding is low (approximately 20%), and it is primarily excreted unchanged in the urine. Serum half-life in infants older than 2 months of age is approximately 2 hours.

ABOUT

Special Considerations/Preparation

Available as powder for injection in 500-mg, 1-g, and 2-g vials. For IM use, reconstitute 500-mg or 1-g vial with 1.3 mL or 2.4 mL of compatible diluent (sterile water for injection, NS, D_5W, lidocaine 0.5% or 1%, or sterile bacteriostatic water for injection) respectively, to a concentration of 280 mg/mL. For IV use, reconstitute 500-mg vial with 5 mL and 1-g vial with 10 mL of compatible diluent to a concentration of 100 mg/mL. Reconstitute 2-g vial with 10 mL of compatible diluent to a concentration of 160 mg/mL. Further dilute reconstituted

solution in compatible infusion solution to a concentration of 1 to 40 mg/mL. Reconstituted solution and solution for infusion are stable for 24 hours at room temperature and 7 days refrigerated [1].

DOSING/ADMINISTRATION

Dose

Disseminated Gonococcal Infections and Gonococcal Scalp Abscesses: 25 mg/kg/dose IV or IM every 12 hours for 7 days, with a duration of 10 to 14 days if meningitis is documented [1].

Meningitis:
0 to 7 days of age: 100 to 150 mg/kg/day IV divided every 8 to 12 hours. Consider smaller doses and longer intervals for very low-birth weight neonates (less than 2 kg) [2].
8 days or older: 150 to 200 mg/kg/day IV divided every 6 to 8 hours. Consider smaller doses and longer intervals for very low-birth weight neonates (less than 2 kg) [2].

Sepsis: The following recommendations were based on developmental pharmacokinetic-pharmacodynamic analysis (n=100) to achieve time above MIC (2 mg/L for postnatal age younger than 7 days and 4 mg/L for postnatal age 7 days or older) of 75% [3]:

Gestational Age (weeks)	Postnatal Age (days)	Regimen
All weeks	younger than 7 days	50 mg/kg/dose IV every 12 hours
Less than 32 weeks	7 days or older	50 mg/kg/dose IV every 8 hours
32 weeks or more	7 days or older	50 mg/kg/dose IV every 6 hours
Leroux, 2016		

Usual dose for bone and joint, genitourinary, intra-abdominal, lower respiratory tract, or skin and skin structure infection [4]
7 days or younger and any weight: 50 mg/kg/dose IV/IM every 12 hours [5].
8 days to 28 days and 2 kg or less: 50 mg/kg/dose IV/IM every 8 to 12 hours [5].
8 days to 28 days and more than 2 kg: 50 mg/kg/dose IV/IM every 8 hours [5].

Uses

Disseminated gonococcal infections and gonococcal scalp abscesses The recommended regimen is ceftriaxone or cefotaxime [1].

Infective endocarditis: The following recommendations are based on a consensus of

experts [7]. The full pediatric guidelines can be found here: https://doi.org/10.1161/CIR.0000000000000298

Organism Directed Therapy		
Organism	First-Choice	Alternative Choice
Streptococci		
Highly susceptible to penicillin G (MBC 0.1 mcg/mL or less); includes most viridans streptococci, groups A, B, C, G nonenterococcal, group D streptococci (S bovis, S equinus)	Penicillin G or CefTRIAXone	Vancomycin or First-generation cephalosporin or CefTRIAXone
Relatively resistant to penicillin (MBC 0.2 mcg/mL or more); less-susceptible viridans streptococci or enterococci	Penicillin G or Ampicillin + Gentamicin (for first 2 weeks, or entire course for enterococci)	Vancomycin + Gentamicin for enterococci Ampicillin + CefTRIAXone (for aminoglycoside (AMG)-resistant enterococci or AMG-intolerant patient) CefTRIAXone + gentamicin (not for enterococcal endocarditis)
Resistant to penicillin	Consult an infectious disease specialist.	---
Staphylococci (S aureus or coagulase-negative staphylococci) †		
Penicillin G susceptible (1 mcg/mL or less) (rare)	Penicillin G	Oxacillin or Nafcillin or First-generation cephalosporin or Vancomycin
Penicillin G resistant (0.1 mcg/mL)	Oxacillin or Nafcillin with or	Vancomycin (for those highly allergic to beta-

	without Gentamicin	lactam antibiotics) or First-generation cephalosporin
Oxacillin (MRSA) resistant (4 mcg/mL)	Vancomycin	Daptomycin for right-sided endocarditis, maybe for left-sided
Vancomycin resistant or intolerant	Daptomycin	Unknown
	†When prosthetic material present add riFAMpin + gentamicin (for first 2 weeks) for all staphylococci	
Gram-negative enteric bacilli	CefTAZidime or Cefepime or Cefotaxime or CefTRIAXone Plus gentamicin (or tobramycin or amikacin, depending on susceptibility)	Broad-spectrum penicillin Plus gentamicin (or tobramycin or amikacin)
HACEK group	CefTRIAXone or Cefotaxime or Ampicillin-sulbactam	Ampicillin (when susceptible) Plus aminoglycoside
KEY: AMG = aminoglycosides; HACEK = Haemophilus species, Aggregatibacter species, Cardiobacterium hominis, Eikenella corrodens, and Kingella species; MBC = minimum bactericidal concentration, MRSA = methicillin-resistant Staphylococcus aureus (includes resistance to oxacillin, nafcillin, and cephalosporins)		
Baltimore, 2015		

Meningitis: Empiric agents for the treatment of meningitis in neonates are ampicillin, gentamicin, and cefotaxime [8]. Reassess therapy based on culture and sensitivity results [2].

Sepsis caused by susceptible gram-negative organisms (e.g. *E coli*, *H influenzae,*and *Klebsiella)*. Optimal treatment for suspected, early-onset sepsis is broad-spectrum antimicrobial coverage using a combination of ampicillin and an aminoglycoside (usually

gentamicin); once a pathogen is identified, therapy should be narrowed unless synergism is required [9].

Duration:

•Procalcitonin values in addition to perinatal risk factors, signs and symptoms, and laboratory values may aid in the determination to discontinue antibiotic therapy in neonates with suspected early-onset sepsis. The duration of antibiotic therapy was reduced by 9.9 hours with a procalcitonin-guided algorithm compared with standard care in a multicenter randomized control trial of 1710 neonates born after 34 weeks of gestational age with possible or unlikely sepsis. Re-infection and mortality was not different between the groups (risk difference 0.1% (95% CI, -5.2% to 5.3%)) [10].

Pediatric FDA Approved Indications

Lower respiratory tract infections (including pneumonia) caused by *Streptococcus pneumoniae*, *S pyogenes* and other streptococci (excluding enterococci), *Staphylococcus aureus* (penicillinase and non-penicillinase producing), *Escherichia coli*, *Klebsiella* species, *Haemophilus. influenzae* (including ampicillin resistant strains), *H parainfluenzae*, *Proteus mirabilis*, *Serratia marcescens*, *Enterobacter* species, indole positive *Proteus* and *Pseudomonas* species (including *P aeruginosa*) [4].

Genitourinary infections (urinary tract infections) caused by *Enterococcus* species, *S epidermidis*, *S aureus* (penicillinase and non-penicillinase producing), *Citrobacter* species, *Enterobacter* species, *E coli*, *Klebsiella* species, *P mirabilis*, *P vulgaris*, *P stuartii*, *M. morganii*, *P rettgerr*, *S marcescens*, and *Pseudomonas* species (including *P. aeruginosa*). Also uncomplicated gonorrhea (cervical/urethral and rectal) caused by *N. gonorrhoeae*, including penicillinase-producing strains [4].

Bacteremia/sepsis caused by *E coli*, *Klebsiella* species, and *S marcescens*, *S aureus*, and *Streptococcus* species (including S pneumoniae) [4].

Skin and skin structure infections caused by *S aureus* (penicillinase and non-penicillinase producing), *S epidermidis*, *S pyogenes* and other streptococci, *Enterococcus* species, *Acinetobacter* species, *E. coli*, *Citrobacter* species (including *C freundii*), *Enterobacter* species, *Klebsiella* species, *P. mirabilis*, *P vulgaris*, *M. morganii*, *P rettgerr*, *Pseudomonas* species, *S marcescens*, *Bacteroides* species, and anaerobic cocci (including *Peptostreptococcus* species and *Peptococcus* species) [4].

Intra-abdominal infections caused by *Streptococcus* species, *E. coli*, *Klebsiella* species, *Bacteroides* species, anaerobic cocci (including *Peptostreptococcus* species and *Peptococcus* species), *P mirabilis*, and *Clostridium* species [4]. Cefotaxime plus metronidazole is considered an appropriate combination antibiotic regimen for pediatric patients with a complicated extra-biliary intra-abdominal infection [11].

Bone and/or joint infections caused by *S aureus* (penicillinase and non-penicillinase producing), *Streptococcus* species (including *S pyogenes*), *Pseudomonas* species (including *P aeruginosa*), and *P mirabilis* [4].

Central nervous system infections (eg, meningitis and ventriculitis) caused by *N meningitidis*, *H influenzae*, *S pneumoniae*, *K pneumoniae*, and *E coli* [4].

Administration

May be given by IM injection, IV push (over 3 to 5 minutes), or intermittent IV infusion. For IV push, a concentration of 50 to 100 mg/mL may be used. For intermittent IV infusion, dilute to a concentration of 10 to 40 mg/mL and infuse over 10 to 30 minutes [6].

MEDICATION SAFETY

Contraindications/Precautions

Extravasation, including extensive perivascular, may occur causing tissue damage requiring surgical intervention [4]
Use cautiously in patients with a **history of gastrointestinal disease**, especially colitis [4]
Clostridium difficile-associated diarrhea, ranging from mild diarrhea to fatal colitis, has been reported. Discontinuation may be required [4]
Leukopenia, neutropenia, or granulocytopenia and in rare cases **bone marrow failure, pancytopenia, or agranulocytosis** may occur [4]
Increased risk of **allergic reaction** including serious reactions requiring medical intervention in patients with previous hypersensitivity to penicillins, other drugs, or other demonstrated allergy [4]
Drug-resistant bacteria may develop if used in the absence of bacterial infection [4]
Use caution in the presence of **renal insufficiency**. Dose reductions are recommended with CrCL less than 20 mL/min/1.73 m(2) [4]
Rapid bolus injection via a central venous catheter has resulted in life-threatening arrhythmias [4]
A **false-positive** reaction for urine glucose may occur with copper reduction test. Enzyme-based tests for glycosuria are recommended [4]

Adverse Effects

Side effects are rare but include rash, phlebitis, diarrhea, leukopenia, granulocytopenia, and eosinophilia.
In a prospective cohort study (n=4579), third generation cephalosporins started by day 3 of life in extremely low birth weight infants (less than 1000 g) were associated with a significantly increased risk of candidiasis compared with other antibiotics [12].

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Acyclovir, alprostadil, amikacin, aztreonam, caffeine citrate, cimetidine, clindamycin, famotidine, gentamicin, heparin, lorazepam, magnesium sulfate, metronidazole, midazolam, milrinone, morphine, oxacillin, penicillin g, potassium chloride, propofol, and remifentanil.

Terminal Injection Site Incompatibility

Azithromycin, fluconazole, protamine sulfate, sodium bicarbonate, and vancomycin.

Monitoring

Measuring serum concentration is not usually necessary. Periodic CBC.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action: Cefotaxime is one of many third-generation cephalosporin antibiotics. The mechanism of action appears to be by bacterial cell wall disruption.

Pharmacokinetics
Metabolized in the liver to an active compound, desacetylcefotaxime. The drug distributes widely (i.e. CSF, bile, bronchial secretions, lung tissue, ascitic fluid, middle ear). Excreted renally as unchanged drug (20% to 36%) and active metabolite (15% to 25%) [6].

Vd: 0.64 L/kg in 100 infants with a median postnatal age of 9 days (0 to 69 days), median gestational age of 31.5 weeks (23 to 42 weeks), postmenstrual age of 33 weeks (25 to 44 weeks), and birth weight of 1,415 g (512 g to 3,990 g) [3].
CL: 0.12 L/kg/hr (0.04 to 0.26 L/kg/hr) in 100 infants with a median postnatal age of 9 days (0 to 69 days), median gestational age of 31.5 weeks (23 to 42 weeks), postmenstrual age of 33 weeks (25 to 44 weeks), and birth weight of 1,415 g (512 g to 3,990 g) [3].
Half-life: 3.63 hours (1.67 to 10.35 hours) in 100 infants with a median postnatal age of 9 days (0 to 69 days), median gestational age of 31.5 weeks (23 to 42 weeks), postmenstrual age of 33 weeks (25 to 44 weeks), and birth weight of 1,415 g (512 g to 3,990 g) [3].

ABOUT

Special Considerations/Preparation

Available as powder for injection in 500-mg, 1-g, and 2-g vials.
Reconstitution
For IM use: Dilute the 500-mg, 1-g, and 2-g vials with 2, 3, and 5 mL of sterile water for injection or bacteriostatic water for injection, respectively, for concentrations of 230, 300, and 330 mg/mL, respectively.
For IV use: Dilute the 500-mg, 1-g, and 2-g vials with 10 mL of sterile water for injection to yield concentrations of 50, 95, and 180 mg/mL, respectively.
Storage: Reconstituted solution for IV use is stable for 24 hours at room temperature and 7 days refrigerated. [6].

DOSING/ADMINISTRATION

Dose

90 to 100 mg/kg/day IV divided every 8 hours [1][2][3].

Uses

Use in neonates is generally limited to treatment of skin, intra-abdominal and urinary tract infections caused by susceptible bacteria - anaerobes (e.g. *Bacteroides fragilis)*, gram positives (e.g. *Staphylococcus aureus*, *Streptococcus pneumoniae*, and other streptococci except enterococcus) and gram negatives (e.g. *Haemophilus influenzae, Klebsiella* species, *E. coli, Proteus vulgaris*, and *Neisseria gonorrhoeae*).

Administration

Give as an intermittent IV infusion at a concentration of 10 to 40 mg/mL over 15 to 60 minutes [4];[5][1][6].

MEDICATION SAFETY

Adverse Effects

Adverse effects are rare. Transient eosinophilia and elevation of hepatic transaminases have been reported in less than 3% of treated patients. Severe overdose can cause tachypnea, pallor, hypotonia, and metabolic acidosis.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Acyclovir, amikacin, aztreonam, cimetidine, clindamycin, dopamine, famotidine, fluconazole, gentamicin, heparin, insulin, lidocaine, linezolid, magnesium sulfate, metronidazole, morphine, multivitamins, oxacillin, penicillin g, potassium chloride, propofol, ranitidine, remifentanil, sodium bicarbonate, and tobramycin.

Terminal Injection Site Incompatibility

Erythromycin lactobionate, sodium bicarbonate, and vancomycin.

Monitoring

Serum concentrations are not routinely monitored.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Broad spectrum bactericidal second generation cephalosporin that has enhanced activity against anaerobic bacteria. Inhibits bacterial cell wall synthesis by binding to one or more penicillin-binding proteins. Not inactivated by β-lactamase. Poor CNS penetration. Highly protein bound. Renally excreted as unchanged drug (85 to 90%). Half-life in term neonates is approximately 1.4 hours, and 2.3 hours in preterm neonates --considerably longer than children (0.6 hours) and adults (0.8 hours).

ABOUT

Special Considerations/Preparation

Available as powder for injection in 1-g and 2-g vials.

IV administration: Reconstitute 1-g vial with 9.5 mL sterile water for injection to a concentration of 100 mg/mL. A 40 mg/mL dilution may be made by adding 4 mL of reconstituted solution to 6 mL sterile water for injection, or D_5W. Stable for 18 hours at room temperature or 7 days refrigerated.

DOSING/ADMINISTRATION

Dose

Usual dose: 30 mg/kg/dose IV infusion or IM.
To reduce pain at IM injection site, cefTAZidime may be mixed with 1% lidocaine without epinephrine.

Antibiotic Dosing Chart:
Renal function and drug elimination are most strongly correlated with Postmenstrual Age (PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.

Dosing Interval Chart		
PMA (weeks)	**PostNatal (days)**	**Interval (hours)**
≤29	0 to 28 >28	12 8
30 to 36	0 to 14 >14	12 8
37 to 44	0 to 7 >7	12 8
≥45	ALL	8

Meningitis
0 to 7 days of age: 100 to 150 mg/kg/day IV divided every 8 to 12 hours. Smaller doses and longer intervals may needed for very low-birth weight neonates (less than 2000 g) [1].
8 to 28 days of age: 150 mg/kg/day IV divided every 8 hours. Smaller doses and longer intervals may needed for very low-birth weight neonates (less than 2000 g) [1].

Uses

Treatment of neonatal meningitis and sepsis caused by susceptible gram-negative organisms (e.g. *E coli, H influenzae, Neisseria, Klebsiella,* and *Proteus* species), especially *Pseudomonas aeruginosa*. Resistance among strains of *Serratia* and *Enterobacteriaceae* is increasing.

Infective endocarditis: The following recommendations are based on a consensus of experts [4]. The full pediatric guidelines can be found here: https://doi.org/10.1161/CIR.0000000000000298

Initial Empirical Therapy or Culture-Negative

Endocarditis*		
Unknown Organism	First-Choice	Alternative Choice
Native valve (community acquired)	Ampicillin/sulbactam + gentamicin with or without vancomycin For prosthetic valve involvement, add rifAMPin	Vancomycin + gentamicin
"Late" prosthetic valve infection (more than 1 year after surgery)		
Nosocomial endocarditis associated with vascular cannulae	Vancomycin + gentamicin (with or without rifAMPin if prosthetic material present) + cefepime or cefTAZidime	Unknown
"Early" prosthetic valve endocarditis (1 year or less after surgery)		
* Culture-negative endocarditis (CNE): generally, attempt to culture the infecting organism for at least 48 hours. Severely ill children need immediate treatment. Consider infectious disease consultation for CNE		
Baltimore, 2015		

Organism Directed Therapy		
Organism	First-Choice	Alternative Choice
Streptococci		
Highly susceptible to penicillin G (MBC 0.1 mcg/mL or less); includes most viridans streptococci, groups A, B, C, G nonenterococcal, group D streptococci (S bovis, S equinus)	Penicillin G or CefTRIAXone	Vancomycin or First-generation cephalosporin or CefTRIAXone
Relatively resistant to penicillin (MBC 0.2 mcg/mL or more); less-	Penicillin G or Ampicillin + Gentamicin (for first 2 weeks, or	Vancomycin + Gentamicin for enterococci Ampicillin + CefTRIAXone

susceptible viridans streptococci or enterococci	entire course for enterococci)	(for aminoglycoside (AMG)-resistant enterococci or AMG-intolerant patient) CefTRIAXone + gentamicin (not for enterococcal endocarditis)
Resistant to penicillin	Consult an infectious disease specialist.	---
Staphylococci (S aureus or coagulase-negative staphylococci) †		
Penicillin G susceptible (1 mcg/mL or less) (rare)	Penicillin G	Oxacillin or Nafcillin or First-generation cephalosporin or Vancomycin
Penicillin G resistant (0.1 mcg/mL)	Oxacillin or Nafcillin with or without Gentamicin	Vancomycin (for those highly allergic to beta-lactam antibiotics) or First-generation cephalosporin
Oxacillin (MRSA) resistant (4 mcg/mL)	Vancomycin	Daptomycin for right-sided endocarditis, maybe for left-sided
Vancomycin resistant or intolerant	Daptomycin	Unknown
	†When prosthetic material present add riFAMpin + gentamicin (for first 2 weeks) for all staphylococci	
Gram-negative enteric bacilli	CefTAZidime or Cefepime or Cefotaxime or CefTRIAXone Plus gentamicin	Broad-spectrum penicillin Plus gentamicin (or tobramycin or amikacin)

	(or tobramycin or amikacin, depending on susceptibility)	
HACEK group	CefTRIAXone or Cefotaxime or Ampicillin-sulbactam	Ampicillin (when susceptible) Plus aminoglycoside
KEY: AMG = aminoglycosides; HACEK = Haemophilus species, Aggregatibacter species, Cardiobacterium hominis, Eikenella corrodens, and Kingella species; MBC = minimum bactericidal concentration, MRSA = methicillin-resistant Staphylococcus aureus (includes resistance to oxacillin, nafcillin, and cephalosporins)		
Baltimore, 2015		

Administration

Intravenous
•IV push over 3 to 5 minutes at a maximum concentration of [2] 100 mg/mL [3] or 200 mg/mL [2].
•Intermittent IV infusion over 30 minutes at a concentration of 1 to 40 mg/mL [2] as well as 50 mg/mL [3].
Intramuscular
•Deep IM administration into a large muscle mass for less serious infections [2].

MEDICATION SAFETY

Adverse Effects

Reported adverse effects are uncommon but include rash, diarrhea, elevated hepatic transaminases, eosinophilia, and positive Coombs' test.
In a prospective cohort study (n=4579), third generation cephalosporins started by day 3 of life in extremely low birth weight infants (less than 1000 g) were associated with a significantly increased risk of candidiasis compared with other antibiotics [5].

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Acyclovir, amikacin, aminophylline, aztreonam, cimetidine, clindamycin, dobutamine, dopamine, enalaprilat, epinephrine, esmolol, famotidine, furosemide, gentamicin, heparin, ibuprofen lysine, linezolid, metronidazole, milrinone, morphine, potassium chloride, propofol, ranitidine, remifentanil, sodium bicarbonate, tobramycin, and zidovudine.

Terminal Injection Site Incompatibility

Amiodarone, azithromycin, erythromycin lactobionate, fluconazole, midazolam, nicardipine, phenytoin, and vancomycin.

Monitoring

Measuring serum concentration is not usually necessary.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action: CefTAZidime is a third-generation cephalosporin with activity against *Pseudomonas* species. It is bactericidal in action, and inhibits enzymes responsible for cell-wall synthesis [6].

Distribution: Widely in body tissues and fluids (ie, CSF, bile, bronchial secretions, lung tissue, ascitic fluid, middle ear). Protein binding is low (less than 10%) [6].
Excretion: Unchanged in the urine (80% to 90%) [6].
Half-Life (adults): Serum half-life following IV administration is approximately 1.9 hours. Half-life significantly longer in patients with renal impairment [6].

ABOUT

Special Considerations/Preparation

Available as powder for injection in 500-mg and 1-g, 2-g, and 6-g vials.

Intravenous solution: Reconstitute 500-mg vial with 10 mL of sterile water for injection to make a concentration of 50 mg/mL. Reconstituted solution stable for 12 hours at room temperature, 3 days refrigerated.

Intramuscular solution: Prepared by reconstituting 500-mg vial with 2.2 mL of 1% lidocaine without epinephrine or Sterile Water to a concentration of 200 mg/mL. Solution is stable for 12 hours at room temperature, 3 days refrigerated.

All vials contain sodium carbonate; when reconstituted, carbon dioxide bubbles will form. Using a vented needle may help reduce spraying and leaking.

DOSING/ADMINISTRATION

Dose

KIDs List: Use caution in neonates due to risk of kernicterus [1]
Sepsis: 50 mg/kg IV every 24 hours.

Meningitis: 100 mg/kg IV loading dose, then 80 mg/kg IV every 24 hours.

Gonococcal Infections
Disseminated Gonococcal Infections and Scalp Abscesses: 25 to 50 mg/kg/day IV/IM in a single daily dose for 7 days, with a duration of 10 to 14 days if meningitis is documented [2].
Gonococcal Infection (neonates born to untreated mothers): 25 to 50 mg/kg **(MAX 250 mg)** IV/IM as a single dose [2].
Gonococcal Ophthalmia Neonatorum: 25 to 50 mg/kg **(MAX 250 mg)** IV/IM as a single dose. (Note: topical antibiotic therapy alone is inadequate and is unnecessary if systemic treatment is given) [2]

Salmonella infection, nontyphoidal: 100 mg/kg IV/IM once daily OR 50 mg/kg IV/IM twice daily for 7 to 10 days [3][4]

Salmonella infection, Typhoid fever: 100 mg/kg IV/IM once daily OR 50 mg/kg IV/IM twice daily for 7 to 10 days [5][4]

Shigella infection, resistant to ciprofloxacin: 50 to 100 mg/kg IM once daily for 2 to 5 days [6]

Dose Adjustments
Syphilis, penicillin drug shortage: During periods where aqueous crystalline penicillin G is compromised, the following is recommended (https://www.cdc.gov/std/treatment/drug-notices.htm): [2]
• For confirmed or highly probable congenital syphilis, check local sources for aqueous crystalline penicillin G (potassium or sodium) and notify the CDC and FDA of limited supply. If IV penicillin G is limited, substitute some or all daily doses with procaine penicillin G (50,000 units/kg IM daily for 10 days)
• If aqueous or procaine penicillin G is unavailable, cefTRAIXone 50 to 75 mg/kg IV daily may be considered in cases with thorough clinical and serologic follow-up and in consultation with an expert due to insufficient evidence. Use caution in neonates with jaundice
• Premature neonates with no clinical evidence of congenital syphilis and might not tolerate IM injections due to muscle mass, IV ceftriaxone may be considered in cases with thorough clinical and serologic follow-up and in consultation with an expert. Dosing should be adjusted according to birthweight

Uses

Gonococcal Infections: In neonates born to mothers with untreated gonorrhea and at a high risk for infection, cefTRIAXone is recommended for the treatment of the following: [2]

- **Gonococcal ophthalmia neonatorium**
- **Disseminated gonococcal infection**
- **Gonococcal scalp abscess**
- **Presumptive gonococcal infection**

A single dose of ceftriaxone is also effective for ophthalmia neonatorum prophylaxis when erythromycin ointment is not available [2].

Infective endocarditis: The following recommendations are based on a consensus of experts [8]. The full pediatric guidelines can be found here: https://doi.org/10.1161/CIR.0000000000000298

Organism Directed Therapy		
Organism	First-Choice	Alternative Choice
Streptococci		
Highly susceptible to penicillin G (MBC 0.1 mcg/mL or less); includes most viridans streptococci, groups A, B, C, G nonenterococcal, group D streptococci (S bovis, S equinus)	Penicillin G or CefTRIAXone	Vancomycin or First-generation cephalosporin or CefTRIAXone
Relatively resistant to penicillin (MBC 0.2 mcg/mL or more); less-susceptible viridans streptococci or enterococci	Penicillin G or Ampicillin + Gentamicin (for first 2 weeks, or entire course for enterococci)	Vancomycin + Gentamicin for enterococci Ampicillin + CefTRIAXone (for aminoglycoside (AMG)-resistant enterococci or AMG-intolerant patient) CefTRIAXone + gentamicin (not for enterococcal

		endocarditis)
Resistant to penicillin	Consult an infectious disease specialist.	---
Staphylococci (S aureus or coagulase-negative staphylococci) †		
Penicillin G susceptible (1 mcg/mL or less) (rare)	Penicillin G	Oxacillin or Nafcillin or First-generation cephalosporin or Vancomycin
Penicillin G resistant (0.1 mcg/mL)	Oxacillin or Nafcillin with or without Gentamicin	Vancomycin (for those highly allergic to beta-lactam antibiotics) or First-generation cephalosporin
Oxacillin (MRSA) resistant (4 mcg/mL)	Vancomycin	Daptomycin for right-sided endocarditis, maybe for left-sided
Vancomycin resistant or intolerant	Daptomycin	Unknown
	†When prosthetic material present add riFAMpin + gentamicin (for first 2 weeks) for all staphylococci	
Gram-negative enteric bacilli	CefTAZidime or Cefepime or Cefotaxime or CefTRIAXone Plus gentamicin (or tobramycin or amikacin, depending on susceptibility)	Broad-spectrum penicillin Plus gentamicin (or tobramycin or amikacin)
HACEK group	CefTRIAXone or Cefotaxime or Ampicillin-	Ampicillin (when susceptible) Plus

	sulbactam	aminoglycoside
KEY: AMG = aminoglycosides; HACEK = Haemophilus species, Aggregatibacter species, Cardiobacterium hominis, Eikenella corrodens, and Kingella species; MBC = minimum bactericidal concentration, MRSA = methicillin-resistant Staphylococcus aureus (includes resistance to oxacillin, nafcillin, and cephalosporins)		
Baltimore, 2015		

Meningitis
Treatment of neonatal meningitis caused by susceptible gram-negative organisms (e.g. *E coli, Pseudomonas, Klebsiella, H influenzae*). CefTRIAXone is contraindicated due to the risk of kernicterus in neonates [9]

Salmonella infection, nontyphoidal
Empiric therapy for suspected nontyphoidal *Salmonella* infection is indicated in infants and neonates 3 months or younger [3][10]
• For those who have culture-positive stool, treat patients younger than 3 months for 7 days. Older children generally do not require treatment unless they present as unwell [3]
• For those who have nontyphoidal *Salmonella* bacteremia, perform cerebrospinal fluid examinations in all patients younger than 3 months and treat for 10 days. For older children, CSF examination is only needed if clinically indicated, and treat for 7 days [3].
• For those who have complicated nontyphoidal *Salmonella* infections (meningitis, osteomyelitis), longer durations of therapy (4 to 6 weeks) are necessary[3].

Salmonella infection, Typhoid fever
Empiric therapy for suspected *Salmonella typhi* or *Salmonella paratyphi* infection (typhoid fever) is indicated for all patients [10][4]
Ceftriaxone compared with azithromycin: Rates of clinical cure (97% vs 91%) and microbiological cure (97% and 97%) were not significantly different between children 4 to 17 years of age (N=64) with confirmed typhoid fever treated with ceftriaxone (75 mg/kg/day IM for 7 days; max 2.5 g/day) or azithromycin (10 mg/kg/day orally for 7 days; max 500 mg/day). Notable, 4 patients treated with ceftriaxone experienced infection relapse within 1 month of treatment compared with no azithromycin-treated patients [5].

Shigella infection
Ciprofloxacin is the drug of choice to treat *Shigella* infections. Ceftriaxone is a second-line therapy to be used when local *Shigella* strains are known to be resistant to ciprofloxacin [6].

Sepsis
Treatment of neonatal sepsis caused by susceptible gram-negative organisms (e.g. *E coli, Pseudomonas, Klebsiella, H influenzae*).

Optimal treatment for suspected, early-onset sepsis is broad-spectrum antimicrobial coverage using a combination of ampicillin and an aminoglycoside (usually gentamicin); once a pathogen is identified, therapy should be narrowed unless synergism is required. CefTRIAXone is contraindicated due to the risk of kernicterus in neonates [9].
There was no difference in failure rate between a 7-day vs 10-day duration of empiric treatment with IV cefTRIAXone and amikacin for culture-proven sepsis in 132 neonates, 1.5 kg or more and gestational age 32 weeks or more, who remitted clinically by day 5 in a randomized study. The follow-up period was 28 days. The median age at presentation was 3 days (2 to 4 days) and 56.8% had early-onset sepsis. The majority of organisms in blood cultures were *Klebsiella* spp. (40.9%), *Staphylococcus aureus* (22.7%), *Enterobacter* spp. (16.7%), and MRSA (7.6%) [11].

Administration

Intravenous:Administer over 60 minutes at a concentration of 10 to 40 mg/mL (lower concentrations may be used, if necessary). Do not mix with calcium-containing solutions in the same IV line; precipitation may occur [7]. Avoid administration of calcium-containing solutions or products within 48 hours of the last administration of cefTRIAXone.
Intramuscular: To reduce pain at the injection site, reconstitute with 1% lidocaine without epinephrine to a final concentration of 250 mg/mL or 350 mg/mL.

MEDICATION SAFETY

Contraindications/Precautions

Contraindications[7]

- **Contraindicated in premature neonates.**
- **Contraindicated for use in neonates with hyperbilirubinemia. Displaces bilirubin from albumin binding sites, resulting in higher free bilirubin serum concentrations.**
- **Concurrent administration of cefTRIAXone andIV calcium-containing solutions (including parenteral nutrition) or products in neonates is contraindicated. There have been a small number of fatal cases of cardiorespiratory arrest in young infants, with 6 deaths, associated with concurrent administration of cefTRIAXone and calcium-containing intravenous solutions. In all cases, the cefTRIAXone dose (150 to 200 mg/kg/day) significantly exceeded the FDA recommended dose and/or was administered IV push. Crystalline material was noted in vascular beds on autopsy (lungs and kidneys) in 4 of the 5 infants for which results were available**

- **Lidocaine added to IV cefTRIAXone solutions is contraindicated.**

[7].

Precautions
Serious and occasionally fatal hypersensitivity reactions have occurred [7].
Clostridium difficile associated diarrhea has been reported [7].
Hematologic: Methemoglobinemia has been reported; risk factors are glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites [12].
Hemolytic anemia, resulting in profound morbidity and fatalities, has been reported in children receiving cefTRIAXone. The majority of cases have occurred in patients with immune deficiencies or sickle cell disease; all patients had previous exposure to cefTRIAXone [13][14][15].
Prothrombin time alteration in patients with impaired vitamin K synthesis or low vitamin K stores [7]
Presence of both hepatic dysfunction and renal disease[7].
Pediatric patients are at a greater risk of gallbladder pseudolithiasis (ceftriaxone-calcium precipitates) [7].
Pediatric patients are at a greater risk of ceftriaxone-calcium precipitates in the urinary tract, which may present as urolithiasis, and ureteral obstruction and post-renal acute renal failure[7].
biliary stasis and biliary sludge risk factors, such as preceding major therapy, severe illness, and total parenteral nutrition; increased risk of pancreatitis, possibly secondary to biliary obstruction [7]

Adverse Effects

Eosinophilia, thrombocytosis, leukopenia. Increase in bleeding time. Diarrhea. Increase in BUN and serum creatinine. Increase in AST and ALT. Skin rash. Transient gallbladder precipitations occasionally associated with colicky abdominal pain, nausea, and vomiting.
In a prospective cohort study (n=4579), third generation cephalosporins started by day 3 of life in extremely low birth weight infants (less than 1000 g) were associated with a significantly increased risk of candidiasis compared with other antibiotics [16].

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Solution Incompatibility

Any calcium-containing solution.

Terminal Injection Site Compatibility

Acyclovir, amikacin, amiodarone, aztreonam, clindamycin, famotidine, gentamicin, heparin, linezolid, metronidazole, morphine, potassium chloride, propofol, remifentanil, sodium bicarbonate, and zidovudine.

Terminal Injection Site Incompatibility

Aminophylline, azithromycin, calcium chloride, calcium gluconate, caspofungin, fluconazole and vancomycin.

Monitoring

Monitor prothrombin time in high risk patients (eg, chronic hepatic disease and malnutrition). Frequently monitor coagulation parameters during concomitant vitamin K antagonist therapy. Monitor for signs and symptoms of gallbladder disease [7].
CBC for eosinophilia, thrombocytosis, leukopenia. Serum electrolytes, BUN, creatinine. AST, ALT, bilirubin. Consider abdominal ultrasonography.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

cefTRIAXone is one of many third-generation cephalosporin antibiotics. The drug distributes widely (i.e. CSF, bile, bronchial secretions, lung tissue, ascitic fluid, middle ear). It is eliminated unchanged by both biliary (40%) and renal mechanisms. Serum half-life in premature infants is 5 to 16 hours. Dosage adjustment is necessary only for patients with combined hepatic and renal failure.

ABOUT

Special Considerations/Preparation

Intravenous solution: Available as a powder for injection in 250-mg, 500-mg, 1-g, and 2-g vials. Prepared by reconstituting powder with compatible solution (sterile water for injection, D_5W, or $D_{10}W$) to a concentration of 100 mg/mL.
Reconstituted solution is stable for 2 days at room temperature, 10 days refrigerated. A dark color may appear after reconstitution; however, potency is retained.
To make 40-mg/mL solution add 6.2 mL to the 250-mg vial.

Intramuscular solution: Prepared by reconstituting 250-mg vial with 0.9 mL of 1% lidocaine without epinephrine to a concentration of 250 mg/mL. Solution is stable for 24 hours at room temperature, 3 days refrigerated.

Chloral hydrate

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Oral and rectal products are no longer manufactured in the US [1]. Due to long half-life, unpredictable responses, and reported deaths, chloral hydrate is a poor choice as a sedating agent for procedures [2][3].
25 to 75 mg/kg per dose orally or rectally.

Uses

Oral and rectal products are no longer manufactured in the US[1].
Sedative/hypnotic for short-term use only. Chloral hydrate has no analgesic properties; excitement may occur in patients with pain.

Administration

Oral: Oral preparation should be diluted or administered after a feeding to reduce gastric irritation [4].
Rectal: The oral preparation may be given rectally [5][6].

MEDICATION SAFETY

Contraindications/Precautions

Contraindicated in patients with significant hepatic or renal impairment, and in those with severe cardiac disease. Oral administration not recommended in patients with esophagitis, gastritis, or gastric or duodenal ulcers [7][4].

Adverse Effects

Episodes of bradycardia are more frequent for up to 24 hours after a single dose in former premature infants. Gastric irritation and paradoxical excitement may also occur after a single

dose. Other toxic effects have generally been reported in patients who received either repeated doses at regular intervals or acute overdoses. These effects may persist for days and include CNS, respiratory, and myocardial depression; cardiac arrhythmias; and ileus and bladder atony. Indirect hyperbilirubinemia may occur because trichloroethanol and bilirubin compete for hepatic conjugation.

Monitoring

Assess level of sedation.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Well absorbed from the oral route, with the onset of action in 10 to 15 minutes. Chloral hydrate is rapidly converted by alcohol dehydrogenase to the active and potentially toxic metabolite trichloroethanol (TCEt), which is excreted renally after glucuronidation in the liver. It is also metabolized to trichloroacetic acid (TCA), which is carcinogenic in mice when given in very high doses. Both TCEt (8 to 64 hours) and TCA (days) have long serum half-lives in neonates and accumulate with repeated doses.

ABOUT

Special Considerations/Preparation

Oral and rectal products are no longer manufactured in the US[1].

Chloramphenicol

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

KIDs List: Avoid in neonates (unless serum concentration monitoring is used) due to risk of gray baby syndrome [1]
In very low-birth weight neonates (less than 2000 g), lower doses and less frequent administration are recommended [2].
0 to 7 days of age: 25 mg/kg/day IV once daily [2].
8 to 28 days: 50 mg/kg/day IV divided every 12 to 24 hours [2].

Uses

A wide-spectrum antimicrobial bacteriostatic agent. May be bactericidal to species such as *H influenzae* and *Neisseria meningitidis* .

Anthrax: Chloramphenicol (for **32 weeks or more gestational age**) Should only be used when other options are unavailable. Use as part of a triple regimen for systemic anthrax (meningitis or disseminated infection or meningitis cannot be ruled out). **Duration:** For anthrax, for 2 to 3 weeks or more until stable. Continue antimicrobial course of prophylaxis (usually oral therapy) for up to 60 days[6].

Bacterial meningitis: An alternative agent for bacterial meningitis due to *Streptococcus pneumoniae* when penicillin MIC is less than 0.1 mcg/mL, *Neisseria meningitidis* when penicillin MIC is less than 1 mcg/mL, and *Haemophilus influenza* (β-lactamase negative or positive) [7][2].

Administration

For IV intermittent infusion, dilute to a concentration of 20 to 25 mg/mL in compatible solution and infuse over 15 to 60 minutes [3][4].

In the preparation and administration of injections, the National Institute for Occupational Safety and Health (NIOSH) recommends the use of double gloves and a protective gown. Prepare in a biological safety cabinet or a compounding aseptic containment isolator; eye/face and respiratory protection may be needed. Prepare compounds in a closed system drug transfer device. During administration, if there is a potential that the substance could splash or if the patient may resist, use eye/face protection. Administer certain dosage forms via a closed system drug transfer device [5].

MEDICATION SAFETY

Adverse Effects

Reversible bone marrow suppression, irreversible aplastic anemia. Serum concentration greater than 50 mcg/mL has been associated with the "gray baby" syndrome (ie, abdominal distention, pallid cyanosis, vasomotor collapse; may lead to death within hours of onset). Fungal overgrowth.

Black Box Warning

According to the manufacturer's black box warning, serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur. There have been reports of aplastic anemia which later terminated in leukemia. Blood dyscrasias have occurred after both short-term and prolonged therapy with this drug. It is essential that adequate blood studies be made during treatment. If blood dyscrasias occur, therapy should be discontinued.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Acyclovir, amikacin, aminophylline, ampicillin, calcium chloride, calcium gluconate, dopamine, enalaprilat, esmolol, heparin, hydrocortisone succinate, lidocaine, magnesium sulfate, metronidazole, morphine, nafcillin, nicardipine, oxacillin, penicillin G, pentobarbital, potassium chloride, ranitidine, sodium bicarbonate, and vitamin K_1.

Terminal Injection Site Incompatibility

Erythromycin lactobionate, fluconazole, metoclopramide, phenytoin, and vancomycin.

Monitoring

Close monitoring of serum concentration is mandatory. Small changes in dose and interval can lead to disproportionately large changes in serum concentration. Therapeutic peak serum concentration: 10 to 25 mcg/mL. Monitor CBC and reticulocyte counts. Assess hepatic and renal function.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Both esters (succinate and palmitate) are biologically inactive prodrugs. Hydrolysis to the active compound is erratic in newborns. Metabolized by hepatic glucuronyl transferase. Hepatically and renally eliminated. Inhibits metabolism of phenobarbital, phenytoin, and other agents.

ABOUT

Special Considerations/Preparation

Chloramphenicol succinate is available as powder for injection in a 1-g vial. Contains 52 mg (2.25 mEq) of sodium per gram. Reconstitute with 10 mL sterile water for injection or D_5W to a concentration of 100 mg/mL. For IV intermittent infusion, further dilute to a concentration of 20 to 25 mg/mL in compatible solution.

Chlorothiazide

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Diuresis: 10 to 20 mg/kg/dose orally every 12 hours.

Diabetes insipidus: 5 mg/kg/dose orally every 12 hours [1].
Administer with food (improves absorption).
IV administration not recommended because of a lack of data.
Note: Do not confuse with hydrochlorothiazide.

Uses

Bronchopulmonary dysplasia (BPD): May improve pulmonary function in patients with BPD; typically a thiazide and spironolactone are used together [2]. In oxygen-dependent infants who were on ventilator support over thirty days (n=43), chlorothiazide (40 mg/kg/day orally in 2 divided doses) in combination with spironolactone (4 mg/kg/day orally in 2 divided doses) until supplemental oxygen was discontinued was associated with improved pulmonary function and decreased fractional oxygen requirement, but was not associated with a decrease in duration of oxygen requirement when compared with placebo [3]. Thiazide diuretics may be appropriate for improving lung mechanics in ventilator-dependent preterm infants greater than 3 weeks of age [4][5].

Diabetes insipidus: Thiazide diuretics are recommended to treat central and/or nephrogenic diabetes insipidus [1][6][7][8].

Edema and Hypertension: Diuretic used in treating both mild to moderate edema and mild to moderate hypertension. Effects increased when used in combination with furosemide or spironolactone.

Heart Failure: In neonates with pulmonary hypertension, supportive care with diuretics may be used cautiously for signs of right-sided heart failure [9].

MEDICATION SAFETY

Adverse Effects

Hypokalemia and other electrolyte abnormalities. Hyperglycemia. Hyperuricemia.
Do not use in patients with significant impairment of renal or hepatic function.

Solution Compatibility

D_5W and NS.

Terminal Injection Site Compatibility

Alprostadil.

Monitoring

Serum electrolytes, calcium, phosphorus, and glucose; urine output and blood pressure.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Limited data in neonates. Variable absorption from GI tract. Onset of action within 1 hour. Elimination half-life depends on GFR, and is approximately 5 hours. Major diuretic effect results from inhibition of sodium reabsorption in the distal nephron. Increases urinary losses of sodium, potassium, magnesium, chloride, bicarbonate, and phosphorus. Decreases renal excretion of calcium. Inhibits pancreatic release of insulin. Displaces bilirubin from albumin binding sites.

ABOUT

Special Considerations/Preparation

Available: 250 mg/5mL suspension for oral use and 500-mg vial as lyophilized powder for injection.

Preparation of IV
Reconstitute 500-mg vial with 18 mL (never less) of sterile water for injection to make a concentration of 28 mg/mL. Use solution immediately after reconstitution; discard unused portion. May further dilute in compatible solution for IV infusion (D_5W and NS).

Cimetidine

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

2.5 to 5 mg/kg/dose every 6 to 12 hours orally or IV infusion over 15 to 20 minutes.

Uses

Prevention and treatment of stress ulcers and GI hemorrhage aggravated by gastric acid secretion.
Apnea of prematurity: Reducing gastric acidity or increasing gastric motility for the sole purpose to reduce apnea episodes is not supported by the literature [3].
Crying and irritability: In otherwise healthy term infants, histamine$_2$ receptor antagonists or proton pump inhibitors should not be used for the treatment of crying and distress [4].
Gastroesophageal Reflux (GER): The risks associated with acid reducing agents outweighs the benefits in preterm infants for GER. Acid blocking agents should not be used and if used in preterm infants, use sparingly [5]. In otherwise healthy term infants, histamine$_2$ receptor antagonists or proton pump inhibitors should not be used for the treatment of visible regurgitation [4].
Gastroesophageal Reflux Disease (GERD): Proton pump inhibitors (PPIs) are the first-line agents for erosive esophagitis in infants and children with GERD. Histamine$_2$ receptor antagonists are the second-line agent if PPIs are not available or are contraindicated. A duration of treatment for 4 to 8 weeks for GERD symptoms is recommended. Regularly reassess the need for long-term acid suppression. If no response after 4 to 8 weeks, then re-evaluate for other causes of symptoms. H_2RAs and PPIs are not recommended for extraesophageal symptoms (e.g. cough, wheezing, asthma), unless GERD symptoms are present and/or GERD has been diagnosed [4].
A trial use of PPIs as a diagnostic test for GERD is not recommended in infants or in patients presenting with extraesophageal symptoms. However, in children with typical GERD symptoms, a trial of 4 to 8 weeks with a PPI may be used as a diagnostic test [4].

Administration

Intermittent IV infusion: Dilute in D_5W or other compatible solution to a final concentration of 6 mg/mL and infuse over 15 to 20 minutes [1].
Oral: Administer doses with meals and at bedtime. Do not administer simultaneously with antacids since antacids may interfere with cimetidine absorption [2].

MEDICATION SAFETY

Contraindications/Precautions

CONTRAINDICATIONS
Contraindicated in patients receiving cisapride due to precipitation of life-threatening arrhythmias. Cardiac arrhythmias and hypotension have been reported following the rapid IV bolus administration of cimetidine [2].

PRECAUTIONS
Infection: Increased risk of infections (necrotizing enterocolitis, pneumonia, upper respiratory tract infections, sepsis, urinary tract infections, and *Clostridium difficile* infections) in infants and children on H_2 blockers or PPIs demonstrated in case-control studies [4][7].

Adverse Effects

Known adverse effects of cimetidine in adults include mental confusion, seizures, thrombocytopenia, neutropenia, nausea, vomiting, diarrhea, gynecomastia, rash, and muscular pain. Cimetidine has been reported to increase the serum level and potentiate toxicity of other drugs such as chlordiazepoxide, diazepam, lidocaine, metronidazole, nifedipine, phenytoin, propranolol, theophylline, warfarin, and certain tricyclic antidepressants [2][8][9].

The use of H2-blockers in preterm infants has been associated with facilitating *Candida* species colonization [10], and an increased risk for late-onset bacterial and fungal sepsis [11][10].
In a prospective, multicenter, observational study comparing VLBW neonates receiving raNITIdine (n=91) to those not receiving raNITIdine (n=183), neonates receiving raNITIdine had an increased rate of infection (37.4% versus 9.8%; OR 5.5; 95% CI, 2.9 to 10.4), increased risk for NEC (9.8% versus 1.6%; OR 6.6; 95% CI, 1.7 to 25), and increased mortality (9.9% versus 1.6%) [12].
In a retrospective, case-control study, H2-blocker use in VLBW infants was associated with an increased incidence of NEC (OR 1.7; 95% CI, 1.34 to 2.19) [13].

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Acetazolamide, acyclovir, amikacin, aminophylline, ampicillin, atropine, aztreonam, caffeine citrate, cefotaxime, cefoxitin, ceftazidime, clindamycin, dexamethasone, diazepam, digoxin, enalaprilat, epinephrine, erythromycin lactobionate, esmolol, fentanyl, fluconazole, flumazenil, furosemide, gentamicin, glycopyrrolate, heparin, insulin, isoproterenol, lidocaine, linezolid, lorazepam, meperidine, meropenem, metoclopramide, midazolam, milrinone, morphine, nafcillin, nicardipine, nitroprusside, pancuronium, penicillin G, piperacillin/tazobactam, potassium chloride, propofol, prostaglandin E_1 , protamine, remifentanil, sodium bicarbonate, vancomycin, vecuronium, vitamin K_1, and zidovudine.

Terminal Injection Site Incompatibility

Amphotericin B (Immediate precipitation occurs), cefazolin, cefepime, indomethacin, and pentobarbital.

Monitoring

Consider esophageal pH monitoring to assess for efficacy (pH greater than 4) [6]. Observe for impaired consciousness and reduced spontaneous movements.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Inhibits gastric acid secretion by histamine H_2-receptor antagonism. Peak inhibition occurs in 15 to 60 minutes after both oral and IV administration. Metabolized in the liver via sulfation and hydroxylation to inactive compounds that are 90% renally eliminated. Half-life in neonates is 1.1 to 3.4 hours, and is prolonged in patients with renal or hepatic insufficiency. The sulfoxide metabolite may accumulate in the CNS and cause toxicity. Antacids interfere with absorption; therefore, concomitant administration is not recommended.

ABOUT

Special Considerations/Preparation

Available as a 150-mg/mL injectable solution in 2-mL single-use vials and 8-mL multidose vials. A 15-mg/mL dilution may be made by adding 1 mL of 150 mg/mL concentration to 9 mL of preservative-free normal saline. Dilution stable for 48 hours. Manufacturer's oral

solution (60 mg/mL) contains 2.8% alcohol. A 2.4 mg/mL oral dilution may be prepared by adding 1 mL (60 mg) of manufacturer's oral solution to 24 mL of sterile water. Stable for 14 days refrigerated. Also available in 200-, 300-, 400-, and 800-mg tablets.

DOSING/ADMINISTRATION

Dose

FDA Dosage
Serious Infections (Caused by Susceptible Strains of Designated Organisms in Certain Conditions)
Younger than 1 month
Usual dosage: 15 to 20 mg/kg/day IV divided into 3 to 4 equal doses [1]
Postmenstrual Age 32 Weeks or Less
Usual dosage: 5 mg/kg IV every 8 hours [1]
Postmenstrual Age 32 to 40 Weeks
Usual dosage: 7 mg/kg IV every 8 hours [1]

Literature-Based Dosage:
Antibiotic Dosing Chart:
Renal function and drug elimination are most strongly correlated with Postmenstrual Age (PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.

Dosing Interval Chart		
PMA (weeks)	**PostNatal (days)**	**Interval (hours)**
≤29	0 to 28 >28	12 8
30 to 36	0 to 14 >14	12 8
37 to 44	0 to 7 >7	12 8
≥45	ALL	6

Anthrax:[2]
32 up to 34 weeks gestational age
0 to 1 week of age: 5 mg/kg/dose IV or orally every 12 hours
1 to 4 weeks of age: 5 mg/kg/dose IV or orally every 8 hours
34 weeks gestational age or older
0 to 1 week of age: 5 mg/kg/dose IV or orally every 8 hours
1 to 4 weeks of age: 5 mg/kg/dose IV or orally every 6 hours
Duration: Duration: For 14 days or longer until stable as combination therapy for systemic anthrax when meningitis is ruled out. For 2 to 3 weeks or more until stable as triple therapy for systemic anthrax (anthrax meningitis or disseminated infection and meningitis cannot be ruled out). For naturally-acquired cutaneous infection, 7 to 10 days. Continue antimicrobial course of prophylaxis (usually oral therapy) for up to 60 days [2].

Congenital toxoplasmosis
• **Dosage:** 5 to 7.5 mg/kg orally/IV every 6 hours **(MAX 600 mg/dose)**[3]
• **Concomitant medications:** Pyrimethamine 2 mg/kg orally once daily for 2 days, then 1 mg/kg orally once daily for 2 to 6 months, then 1 mg/kg orally 3 times weekly to complete the course of therapy PLUS folinic acid (leucovorin) 110 mg orally 3 times per week during pyrimethamine treatment and for up to 1 week after completing pyrimethamine [4][3]
• **Concomitant medications (if CSF protein 1 g/dL or greater OR severe chorioretinitis in vision threatening area):** PredniSONE 0.5 mg/kg orally every 12 hours until CSF protein is less than 1 g/dL or resolution of severe chorioretinitis. Start predniSONE 48 to 72 hours after the initiation of anti-*Toxoplasma* therapy [4].
• **Duration of therapy, confirmed or strongly suspected cases:** 12 months [4].
• **Duration of therapy, asymptomatic cases with normal fetal ultrasonography and normal postnatal evaluations:** At least 3 months [4].

Dosage Adjustments
Renal Adjustments
• **Mild to moderate impairment:** No adjustment is necessary [1].
• **Severe impairment:** No specific recommendations are available [1].
Hepatic Adjustments
• **Mild to moderate impairment:** No adjustment is necessary [1].
• **Severe impairment:** No specific recommendations are available [1]. Consider increasing the dosing interval in patients with significant liver dysfunction.
Other Adjustments
• **Anaphylactic and severe hypersensitivity reactions:** Discontinue treatment permanently in case of an anaphylactic or severe hypersensitivity reaction [1].
• **Diarrhea:** Discontinue treatment if diarrhea occurs during therapy [1].

Uses

Bacteriostatic antibiotic used for the treatment of bacteremia and pulmonary and deep tissue infections caused by anaerobic bacteria and some gram-positive cocci.
Clindamycin should not be used in the treatment of meningitis due to inadequate perfusion into the CSF [7].

Anthrax[2]:
Postexposure prophylaxis for *Bacillus anthracis***(Oral)**
Penicillin-resistant strains or prior to susceptibility testing
- **Preferred:** Ciprofloxacin. *Alternatives in order of preference: clindamycin, doxycycline (not for neonates 37 weeks gestation or younger), or levofloxacin.*
- **Penicillin-susceptible strains**
- **Preferred:** Amoxicillin. *Alternative: penicillin VK.*

Cutaneous Anthrax treatment, without systemic involvement (Oral)
All strains, regardless of penicillin susceptibility or if susceptibility is unknown
- **Preferred:** Ciprofloxacin. *Alternatives in order of preference: doxycycline (not for*

neonates 37 weeks gestation or younger), clindamycin, levofloxacin.

- **Alternatives for penicillin-susceptible strains**
- **Preferred:** Amoxicillin. *Alternative: penicillin VK.*

Systemic Anthrax when meningitis can be ruled out (IV)
Combination IV Therapy

- **Preferred:** Ciprofloxacin. *Alternatives in order of preference: meropenem, levofloxacin, imipenem/cilastatin, or vancomycin. If strains are penicillin-susceptible, then penicillin G (preferred) or ampicillin (alternative).*
- **Plus**
- **Preferred:** Clindamycin. *Alternatives in order of preference: linezolid, doxycycline (not for neonates 37 weeks gestation or younger), or rifampin.*

Systemic Anthrax (meningitis or disseminated infection and meningitis cannot be ruled out) (IV)
Triple IV Therapy

- **Preferred:** Ciprofloxacin. *Alternatives in order of preference: levofloxacin or moxifloxacin*
- **Plus**
- **Preferred:** Meropenem. *Alternatives in order of preference: imipenem/cilastatin or doripenem. If strains are penicillin-susceptible, then penicillin G (preferred) or ampicillin (alternative).*
- **Plus**
- **Preferred:** Linezolid. *Alternatives in order of preference: clindamycin or rifampin or as a last resort, chloramphenicol*

Oral follow-up therapy for severe anthrax
Combination Oral Therapy

- **Preferred:** Ciprofloxacin. *Alternative: levofloxacin. If strains are penicillin-susceptible, amoxicillin (preferred) or penicillin VK (alternative).*
- **Plus**
- **Preferred:** Clindamycin. *Alternatives in order of preference: doxycycline (not for neonates 37 weeks gestation or younger) or linezolid.*

Toxoplasmosis - HIV co-infection: Pyrimethamine, sulfADIAZINE, and folinic acid are first-line therapy for HIV-infected pediatric patients with toxoplasmosis. In patients that develop a sulfonamide hypersensitivity, clindamycin is the preferred agent to replace sulfADIAZINE. This therapy is recommended for both treatment and secondary prophylaxis of toxoplasmosis [3].

Administration

Infuse IV over 10 to 60 minutes, **not to exceed 30 mg/min**, at a **concentration not to exceed 18 mg/mL**[5]. The recommended standard concentration for neonates is 6 mg/mL [6].

MEDICATION SAFETY

Contraindications/Precautions

Contraindications
Hypersensitivity to other lincosamides, such as lincomycin [1]

Precautions
Gastrointestinal: History of gastrointestinal disease, particularly colitis [1]
Hepatic: Severe hepatic disease; monitoring recommended [1]
Immunologic: Anaphylactic shock and anaphylactic reactions have been reported; discontinuation required and institute appropriate therapy [1].
Immunologic: Severe and potentially fatal hypersensitivity reactions, including severe skin reactions (eg, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, and Stevens-Johnson syndrome) and anaphylactic reactions, have been reported; discontinue use for any hypersensitivity reaction and provide immediate treatment for anaphylactic reactions [1].
Immunologic: History of atopy [1]
Infection: Superinfection may occur due to overgrowth of nonsusceptible organisms, especially yeast [1].
Renal: Acute kidney injury including acute renal failure may occur; monitoring recommended in patients with preexisting renal dysfunction or taking concomitant nephrotoxic drugs or if therapy is prolonged [1].
Respiratory: Life-threatening or fatal gasping syndrome has been reported with the administration of IV solutions containing benzyl alcohol in neonates, especially in premature or low-birth weight infants or with concomitant medication use [1].

Adverse Effects

Hypersensitivity reactions, jaundice, liver function test abnormalities, and acute kidney injury have been reported in association with clindamycin therapy [1].

Black Box Warning

Clostridioides difficile associated diarrhea (CDAD) has been reported with nearly all antibacterial agents, including clindamycin phosphate, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the

colon, leading to overgrowth of *C difficile*.
Because clindamycin phosphate therapy has been associated with severe colitis which may end fatally, it should be reserved for serious infections where less toxic antimicrobial agents are inappropriate. It should not be used in patients with nonbacterial infections such as most upper respiratory tract infections. *C difficile* produces toxins A and B, which contribute to the development of CDAD. Hypertoxin producing strains of *C difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require a colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.
If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C difficile*, and surgical evaluation should be instituted as clinically indicated [1].

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Acyclovir, amikacin, amiodarone, ampicillin, aztreonam, caffeine citrate, cefazolin, cefepime, cefotaxime, cefoxitin, ceftazidime, ceftriaxone, cimetidine, enalaprilat, esmolol, gentamicin, heparin, hydrocortisone succinate, linezolid, magnesium sulfate, metoclopramide, metronidazole, midazolam, milrinone, morphine, netilmicin, nicardipine, penicillin G, piperacillin, piperacillin/tazobactam, potassium chloride, propofol, prostaglandin E_1, ranitidine, remifentanil, sodium bicarbonate, tobramycin, and zidovudine.

Terminal Injection Site Incompatibility

Aminophylline, azithromycin, barbiturates, caspofungin, fluconazole, and phenytoin.

Monitoring

Therapeutic Laboratory Monitoring
• Monitor CBC periodically in patients on prolonged therapy [8].
• Perform bacteriologic studies (ie, culture and susceptibility) to determine the causative organisms and their susceptibility to clindamycin [8].

Toxic Laboratory Monitoring
• Monitor CBC periodically during prolonged therapy [8].
• Monitor liver tests periodically in patients with severe liver disease and during prolonged therapy [8].
Monitor renal function periodically during prolonged therapy [8].

Toxic Physical Monitoring
• Careful medical history is necessary since *Clostridioides difficile*-associated disease (CDAD) has been reported to occur over two months after the administration of antibacterial agents [8].
• Monitor organ system function in patients up to 16 years of age [8].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Pharmacology Mechanism of Action
Minimum inhibitory Concentrations: The table below lists susceptibility interpretive criteria for clindamycin with various organisms, as recognized by the US Food and Drug Administration (FDA) [9][8] and the Clinical Laboratory Standards Institute (CLSI) [10]:

Pathogen	Minimum Inhibitory Concentration (mcg/mL)		
	Susceptible	Intermediate	Resistant
Staphylococcus spp	0.5 or less	1 to 2	4 or greater
Streptococcus pneumoniae	0.25 or less	0.5	1 or greater
Streptococcus beta-hemolytic group	0.25 or less	0.5	1 or greater
Streptococcus viridans group	0.25 or less	0.5	1 or greater
Anaerobes	2 or less	4	8 or greater

Resistance patterns: Resistance to clindamycin is most often caused by modification of specific bases of the 23S ribosomal RNA [8].
Cross-resistance: Cross-resistance between clindamycin and lincomycin is complete. Because the binding sites for these antibacterial drugs overlap, cross-resistance is sometimes observed among lincosamides, macrolides and streptogramin B. Macrolide-inducible resistance to clindamycin occurs in some isolates of macrolide-resistant bacteria. Macrolide-resistant isolates of staphylococci and beta-hemolytic streptococci should be screened for induction of clindamycin resistance using the D-zone test [8].
Spectrum of activity: Clindamycin is active against the following pathogens in vitro and in vivo [8]:
Gram positive

- Methicillin-susceptible *Staphylococcus aureus*
- Penicillin-susceptible *Streptococcus pneumonia*
- *Streptococcus pyogenes*

Anaerobes
- *Clostridium perfringens*
- *Fusobacterium necrophorum*
- *Fusobacterium nucleatum*
- *Peptostreptococcus anaerobius*
- *Prevotella melaninogenica*

Clindamycin has in vitro activity against the following pathogens; clinical efficacy against these pathogens is unknown [8]
Gram positive
- Methicillin-susceptible *Staphylococcus epidermidis*
- *Streptococcus agalactiae*
- *Streptococcus anginosus*
- *Streptococcus mitis*
- *Streptococcus oralis*

Anaerobes
- *Actinomyces israelii*
- *Clostridium clostridioforme*
- *Eggerthella lenta*
- *Finegoldia (Peptostreptococcus) magna*
- *Micromonas (Peptostreptococcus) micros*
- *Prevotella bivia*
- *Prevotella intermedia*
- *Propionibacterium acnes*

Mechanism of action: Clindamycin inhibits bacterial protein synthesis by binding to the 23S RNA of the 50S subunit of the ribosome. Clindamycin is bacteriostatic [8].

Therapeutic Drug Concentration
AUC
IV, multiple-dose, 5 to 7 mg/kg, pediatric: 52.5 to 55.9 mcg x hr/mL [1]
Peak concentration
• **IV, single-dose, 5 to 7 mg/kg, pediatric:** 10 mcg/mL [8]
• **IV, multiple-dose, 5 to 7 mg/kg, pediatric:** 9 to 10.5 mcg/mL [8]
Time to peak concentration
IV: End of infusion [8]
Trough concentration
IV, multiple-dose, 5 mg/kg to 7 mg/kg, pediatric: 4.4 to 4.6 mcg/mL [1]

Distribution
Tissue fluids
Blood-brain barrier: Does not cross [11]

Metabolism
Sites and kinetics
Liver and intestine: Extensive [8]
Metabolites
• **Clindamycin sulfoxide** (major) [8]
• **N-desmethylclindamycin** (minor) [8]
Metabolic enzymes and transporters: Substrate of CYP3A [8]

Excretion
• **Hemodialysis removal:** No [8]
• **Peritoneal dialysis removal:** No [8]

Elimination Half-Life
IV/IM: 2.5 to 3 hours [8]

ABOUT

Special Considerations/Preparation

Oral
Availability: Clindamycin palmitate hydrochloride granules for solution to make 75mg/5mL (15 mg/mL) solution when reconstituted with water [12]
Storage: Store at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F). Do not refrigerate reconstituted solution. The solution is stable for 2 weeks at room temperature [12].

IV
Availability: 150 mg/mL solution in 2-, 4-, 6-mL vials containing 9.45 mg of benzyl alcohol.
Storage:
• Store vials at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F). Discard unused contents of vial within 24 hours of entry [1].
• Store IV solution diluted with dextrose 5% in Galaxy plastic containers at a room temperature of 25 degrees C. Avoid exposure to temperatures greater than 30 degrees C [1].
Preparation
• Do not inject undiluted as a bolus [8].
• Dilute with D5W or NS to a concentration no greater than 18 mg/mL; doses of 300 and 600 mg should be diluted with 50 mL of diluent; doses of 900 and 1200 mg should be diluted with 100 mL of diluent [8].

DOSING/ADMINISTRATION

Dose

Neonatal Abstinence Syndrome; Adjunct
35 weeks GA or older: Initial, 0.5 to 1 mcg/kg, followed by 0.5 to 1.25 mcg/kg/dose orally every 4 to 6 hours [1][2][3][4]. Discontinue based on NAS scores and patient stability.

Uses

Neonatal abstinence syndrome, adjunct: CloNIDine has been used as an adjunct to tincture of opium in neonates with intrauterine exposure to heroin or methadone. In a prospective, randomized, double-blind, placebo-controlled trial, infants 35 weeks GA and older receiving tincture of opium with oral cloNIDine experienced fewer treatment failures, a shorter duration of treatment and observation, and required less tincture of opium than infants receiving tincture of opium with placebo. There were no clinically important changes in blood pressure and heart rate in the cloNIDine group [4]. In a prospective, randomized, open-label trial, infants 35 weeks gestational age or older treated with morphine for NAS experienced shorter morphine treatment days (4.6 less days (95% CI, 0.3 to 8.9 days)) and no difference in morphine total dose with adjunctive phenobarbital compared with cloNIDine. However, the total duration of phenobarbital therapy continued for an average of 3.8 months (range 1 8 months) [5].
Sublingual buprenorphine was associated with the largest reduction in length of treatment and length of stay for NAS in a network meta-analysis of 18 randomized controlled trials (number of participants=1072) of buprenorphine, clonidine, diluted tincture of opium and clonidine, diluted tincture of opium, morphine, methadone, and phenobarbital. Morphine was the least effective opioid [6]. The findings should be interpreted with caution due to significant study limitations [6][7].

Neonatal abstinence syndrome (NAS), monotherapy: Overall, cloNIDine monotherapy for NAS appeared to be as effective as morphine in a randomized, double-blind, pilot study of 31 neonates younger than 7 days (gestational age, 35 weeks or more). Rescue drugs were not necessary in any neonate. The initial cloNIDine dose was 0.625 mcg/kg/dose orally every 3 hours with dose titrations up to a maximum of 12 mcg/kg/day [8].

Sedation and analgesia, Adjunct; Mechanical ventilation: There is a lack of evidence to support the use in term and preterm newborn infants. There was no improvement in mortality, duration of mechanical ventilation or intensive care unit stay between the cloNIDine (1 mcg/kg/hr) and placebo group in a study of 112 term infants [9].

Administration

Oral: Some experts recommend using a dilution of the epidural formulation of cloNIDine for use in neonates with NAS due to concerns about extemporaneous compounded oral suspensions and accuracy of dosing [3][4]. The epidural formulation (100 mcg/mL) was diluted in NS to a concentration of 5 mcg/mL and used orally in a randomized controlled trial [4].

MEDICATION SAFETY

Contraindications/Precautions

Epidural Injection
Contraindicated in patients with an injection site infection, patients with a bleeding diathesis, and patients on concurrent anticoagulant therapy. Epidural administration above the C4 dermatome is also contraindicated [10].

Precautions
Abrupt discontinuation may result in symptoms of withdrawal (eg, agitation, headache, tremor, rapid rise of blood pressure); a gradual reduction of dosage is recommended when therapy is discontinued [11].

Adverse Effects

Local anesthetics; adjunct: The use of cloNIDine as an adjunct with local anesthetics for caudal or spinal anesthesia/analgesia has been associated with apnea and respiratory depression in neonates and premature infants [12][13][14][15].

Neonatal abstinence syndrome (NAS): The use of cloNIDine for treatment of NAS has not been associated with clinically important changes in blood pressure or heart rate; however, close monitoring is imperative [16][4]. Adjunct cloNIDine up to doses of 24 mcg/kg/day in neonates at least 35 weeks' gestation resulted in a heart rate decrease between 7 to 10 beats per minute compared with baseline in a retrospective study (n=64). Systolic blood pressure did not significantly change during cloNIDine treatment with any dose, but diastolic blood pressure was significantly increased 5 mm Hg with doses between 1.5 and 2 mcg/kg/dose every 3 hours. After discontinuation of clonidine the blood pressure (systolic and diastolic) increased (8 and 4 mm Hg, respectively) compared with baseline [16].

Monitoring

Monitor heart rate and blood pressure every 4 hours the first 2 days of therapy and every 12

hours thereafter; monitor blood pressure closely for 48 hours after discontinuing cloNIDine to access for rebound hypertension. Monitor NAS scores every 3 to 4 hours during treatment using a published abstinence assessment tool such as the modified Neonatal Abstinence Scoring System (Finnegan) or the Lipsitz tool [2][4].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action: CloNIDine is a centrally acting alpha-2-adrenergic agonist. Stimulation of these alpha-adrenoreceptors in the brain stem results in decreased sympathetic outflow from the CNS and in reductions in peripheral resistance, heart rate, and blood pressure. Its action in ADHD is unknown [11].

Onset and Peak effect: After oral administration, onset of action of hypotension occurs within 30 to 60 minutes with a peak effect within 2 to 4 hours [11].
Tmax: Peak concentrations occur 3 to 5 hours after dosing of immediate-release formulation [11].
Effect of food: Food does not affect the pharmacokinetics [11].
Elimination: Approximately 50% of a dose is metabolized in the liver and approximately 40% to 60% of a dose is eliminated in the urine as unchanged drug [3].
Half-life: Elimination half-life in neonates is 44 to 72 hours [3] and is prolonged in patients with renal impairment [11][17].
Clearance: In neonates, clearance of cloNIDine rapidly increases with postnatal age over the first month of life. Pharmacokinetic modelling showed that by the age of 1 month, neonates had achieved 70% of adult clearance [18].

Extracorporeal membrane oxygenation (ECMO): Clearance doubles and Vd increases by 55% for clonidine in infants on ECMO compared to no ECMO. In 22 infants (median age, 1 month; gestational 38.9 weeks) administered clonidine for sedation, the estimated clearance and Vd were 29.9 L/hr/70 kg and 454 L/70 kg, respectively. The tubing for the ECMO circuit was polyvinyl chloride. The priming volume was 350 mL for the neonates and 900 mL for the pediatric patients. The majority (90%) of infants were also on continuous venovenous hemofiltration. There was no association between the type of ECMO (venovenous or venoarterial) and parameters (volume or clearance) [19].

ABOUT

Special Considerations/Preparation

Oral
Availability: 0.1-, 0.2- and 0.3-mg immediate-release tablets [11].

Extemporaneous Preparation

•CloNIDine **0.01 mg/mL (10 mcg/mL) oral suspension** can be prepared by triturating three 0.1 mg cloNIDine tablets in a glass mortar, then levigating with 1 to 2 mL of **Oral Mix or Oral Mix SF**. Transfer to an amber plastic bottle, rinse mortar and pestle with the vehicle, and add sufficient vehicle for a final volume of 30 mL. The solution stored in amber glass bottles, plastic bottles, or oral plastic syringes is stable for 91 days at 25°C. The solution is stable in amber glass or plastic bottles at 4° C for 91 days[20]. Also when made with **Ora-Blend**, is stable for at least 91 days when stored in clear plastic syringes at either 25°C or 4°C [21]

•CloNIDine **0.01 mg/mL (10 mcg/mL) oral solution** was prepared by dissolving 60 mg of clonidine hydrochloride active substance powder in 5 mL of water for injection and agitating using a magnetic stirrer. **Inorpha® (Inresa)** 95 mL was added and mixed with the magnetic stirrer for 5 minutes. Then 1 mL aliquots were transferred to pre-filled (60 mL) Inorpha® amber polyethylene terephthalate bottles for a final concentration of 10 mcg/mL. Contents were homogenized by 10 repeated inversions. The solution remained stable for 60 days at 5°C. The solution also remained stable when pre-stored for 30 days at 5°C, then another 30 days with daily opening. No microbial growth was observed [22].

•CloNIDine **0.02 mg/mL (20 mcg/mL)** oral solution withOUT preservatives [23]:

- Mix 100 mg cloNIDine hydrochloride powder with 100 mL purified water for a 1 mg/mL stock solution
- Mix 2 mL of the cloNIDine stock solution with sufficient quantity of simple syrup (64 g sucrose/36 g water) for a final volume of 100 mL
- Adjust pH to 4 to 5 with citric acid 5% w/v
- Physicochemical stability was noted at 90 days for solutions stored at 5°C, 25°C, and 40°C in unopened or opened (3 times/day) glass amber bottles.
- In opened (3 times/day) glass amber bottles: When stored at 5°C, 25°C, and 40°C, the solutions were microbiologically stable for up to 42 days, 7 days and 28 days.
- In unopened glass amber bottles: When stored at 5°C, 25°C, and 40°C, the solutions were microbiologically stable for up to 90 days.
- Osmolality on day 0 was 1327 mOms/kg-H_2O and a range of 1313 to 1376 mOms/kg-H_2O on day 90.

•CloNIDine **0.02 mg/mL (20 mcg/mL)** oral solution with a preservative: [23]

- Mix 100 mg cloNIDine hydrochloride powder with 100 mL purified water for a 1 mg/mL stock solution
- Stir 150 mg of potassium sorbate with 48 mL of purified water in a beaker
- Mix 2 mL of the cloNIDine stock solution to the potassium sorbate solution
- Add sufficient quantity of simple syrup (64 g sucrose/36 g water) for a final volume of 100 mL
- Adjust pH to 4 to 5 with citric acid 5% w/v
- Physicochemical stability was noted at 90 days for solutions stored at 5°C in unopened or opened (3 times/day) glass amber bottles. CloNIDine degraded to less than 90% at 10 days at 40°C, and within 40 days at 25°C.
- In opened (3 times/day) glass amber bottles: When stored at 5°C, 25°C, and 40°C, the solutions were microbiologically stable for up to 42 days.

- In unopened glass amber bottles: When stored at 5°C, 25°C, and 40°C, the solutions were microbiologically stable for up to 90 days.
- Osmolality on day 0 was 1350 mOms/kg-H_2O and a range of 1360 to 1483 mOms/kg-H_2O on day 90.

•CloNIDine **0.02 mg/mL (20 mcg/mL) oral solution** can be prepared by triturating six 0.1 mg cloNIDine tablets in a glass mortar, then levigating with 1 to 2 mL of simple syrup NF. Transfer to an amber plastic bottle and add sufficient simple syrup for a final volume of 30 mL. The solution is stable for 35 days under refrigeration. No negative effect on neonatal feeding osmolality is expected [24].
•Although a 100 mcg/mL concentration can be prepared, it's not practical when measuring neonate doses. CloNIDine **0.1 mg/mL (100 mcg/mL)** oral suspension can be prepared by grinding thirty (30) 0.2 mg-cloNIDine tablets, adding 2 mL of Purified Water, USP, to make a fine paste, and adding enough Simple Syrup, NF, for a final volume of 60 mL. The suspension is stable for 28 days when refrigerated (4 degrees C) [25].

Epidural Injection
Availability: 100 mcg/mL and 500 mcg/mL epidural injection in 10-mL single-dose vials. Vials are preservative free. The 500 mcg/mL-strength must be diluted with NS to a final concentration not exceeding 100 mcg/mL prior to use. Do not use with preservative-containing diluents [10].

Clopidogrel

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Thrombosis; Prophylaxis
35 weeks of gestation or greater: initial, 0.2 mg/kg orally once daily [1].
In the Platelet Inhibition in Children On cLOpidogrel (PICOLO) trial (n=73; neonates 30 days and younger (n=34) and infants greater than 30 days (n=39)), a clopidogrel dose of 0.2 mg/kg/day given to infants and children (aged 0 to 24 months; 35 weeks of gestation or greater) at risk of arterial thrombosis achieved a similar antiplatelet effect (30% to 50% inhibition of 5 mcmol/L adenosine diphosphate (ADP)-induced platelet aggregation) as a 75 mg/day regimen in adults. A total of 79% of the subjects were taking low-dose aspirin 81 mg or less per day (aspirin mean dose, 8.8 +/- 14 mg/kg/day) [1].

Discontinuation
Clopidogrel should be discontinued 5 days prior to elective surgery if an antiplatelet effect is not desired [2].

Uses

Thromboprophylaxis: Antiplatelet agent for the prophylaxis of thrombotic events [3][4][1]. Has been used successfully for the prophylaxis of thrombosis in cardiac disease and cardiac conditions associated with a high risk for arterial thrombosis [3][1][4].

Pediatric FDA Approved Indications
Not FDA approved in pediatric patients [2].

Administration

May be given without regard to feedings [2].

MEDICATION SAFETY

Contraindications/Precautions

Contraindications

Active, pathological bleeding (eg, peptic ulcer or intracranial hemorrhage) [6]. In one pediatric clinical study (n=17), significant intracranial hemorrhage was reported in 25% of pediatric patients (n=2/9) when clopidogrel was used concomitantly with aspirin [7]. In another study (n=46), 1 case each of severe epistaxis and gastrointestinal bleeding was reported in the 2 children receiving concomitant warfarin and clopidogrel therapy [4]. There was 1 report of massive upper GI bleeding in a child on concomitant clopidogrel, low-dose aspirin, and warfarin in another study (n=15) [5].

Precautions
Administration: Nasogastric administration in critically ill patients after cardiopulmonary resuscitation increases risk of impaired clopidogrel bioavailability [8]
Antiplatelet effect diminished: Patients with impaired CYP2C19 function may experience diminished effectiveness; consider alternative therapy in those identified as CYP2C19 poor metabolizers (eg, approximately 2% of White and 4% of Black patients are poor metabolizers, prevalence is higher in Asian patients [eg, 14% of Chinese]; tests are available to identify such patients) [6]. Also consider alternative therapy in intermediate metabolizers [9][10]
Concomitant use: Avoid with omeprazole or esomeprazole [6]: in a subgroup analysis (n=49) of the Platelet Inhibition in Children On cLOpidogrel (PICOLO) trial, clopidogrel plus a proton pump inhibitor reduced platelet inhibition and reduced the numbers of responders [11]
Concomitant use: Etravirine not recommended [12]
Concomitant use: Avoid use with strong CYP2C19 inducers [6]
Discontinuation: Premature discontinuation may increase risk of cardiovascular events [6] including, stent thrombosis, myocardial infarction, and death, particularly in patients undergoing percutaneous coronary intervention [13]; restart as soon as possible when temporary discontinuation is required [6]
Hematologic: Thrombotic thrombocytopenic purpura, with some cases fatal, has been reported [6]
Hematologic: Bleeding risk is increased with concomitant use of other drugs that increase bleeding (eg anticoagulants, antiplatelet agents, and chronic use of NSAIDs) [6]
Immunologic: Hypersensitivity reactions (including angioedema or hematologic reaction) have been reported, including in patients with a history of hypersensitivity or hematologic reaction to other thienopyridines [6]
Surgery: Interrupt use 5 days prior to elective surgery with major risk of bleeding, when possible [6]

Adverse Effects

Bleeding and thrombotic thrombocytopenic purpura are the most common hematological adverse events [2][4]. Anemia, neutropenia, and leukopenia have also been reported [4].

Black Box Warning

The effectiveness of clopidogrel hydrogen sulfate results from its antiplatelet activity, which is

dependent on its conversion to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. Clopidogrel hydrogen sulfate at recommended doses forms less of the active metabolite and so has a reduced effect on platelet activity in patients who are homozygous for nonfunctional alleles of the CYP2C19 gene, (termed "CYP2C19 poor metabolizers"). Tests are available to identify patients who are CYP2C19 poor metabolizers. Consider use of another platelet P2Y12 inhibitor in patients identified as CYP2C19 poor metabolizers [6].

Monitoring

Measure bleeding time prior to therapy initiation and 3 to 7 days after therapy initiation to assess drug efficacy. Platelet aggregation assay studies may be useful in some patients to evaluate response [5]. Monitor hematological parameters closely during the first few months of therapy and every 2 to 3 months in patients on long-term therapy [4].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action: Clopidogrel is a prodrug that is metabolized to the active form (thiol derivative) which inhibits platelet aggregation by selectively and irreversibly binding to the adenosine diphosphate (ADP) P2Y12 receptor on platelets. This binding prevents activation of the ADP-mediated glycoprotein GPIIb/IIIa complex, which is necessary for platelet aggregation [2].
Pharmacodynamics: This action is irreversible for the remainder of the platelet lifespan (7 to 10 days). Dose-dependent inhibition of platelet aggregation can be seen 2 hours after single oral doses. Platelet inhibition reaches steady state at days 3 to 7 after therapy initiation. Platelet aggregation and bleeding time gradually return to baseline values after treatment is discontinued, generally in about 5 days [2].

Bioavailability: at least 50%; food does not affect absorption. Peak concentration achieved 30 to 60 minutes after administration [2].
Metabolism: Extensively metabolized by two main metabolic pathways: one mediated by esterases and leading to hydrolysis into an inactive carboxylic acid derivative (85% of circulating metabolites) and one mediated by multiple cytochrome P450 enzymes (CYP2C19, CYP3A, CYP2B6 and CYP1A2). The active thiol metabolite binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation for the lifespan of the platelets [2].
Elimination: Approximately 50% and 46% is eliminated in the urine and feces, respectively [2].
Half-life: Clopidogrel, 6 hours (75-mg dose in adults); active metabolite, 30 minutes [2].

ABOUT

Special Considerations/Preparation

Available: 75-mg and 300-mg tablets [2].
Extemporaneous Compound (oral suspension): Triturate four 75-mg tablets in a mortar and mix with 30 mL of Ora-Plus and 30 mL of Ora-Sweet for a final concentration of 5 mg/mL. Suspension is stable for 60 days at room temperature or refrigerated.**Shake well** before use [14].

Colistin

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Aerosolized/nebulization
Not an approved route and there are no strong data to support dose recommendations. See USES section for more information.

IV
Gram-negative infections: 2.5 to 5 mg/kg/day of colistin base IV or IM in 2 to 4 divided doses, depending on severity of infection. **Maximum: 5 mg/kg/day of colistin base activity** in patients with normal renal function [1]. Doses of 5 mg/kg/day colistin base may be inadequate; average concentration was 1.1 mcg/mL after a single IV dose of 5 mg/kg in 7 neonates (median 38 weeks gestation and 13 days postnatal age) in the neonatal intensive care unit [2].

Dosage Adjustment
Renal impairment: There are no data available for pediatric patients with renal impairment; however, the following dose adjustments are based on recommendations for adults with renal impairment [1]:

- 50 to 79 mL/min: 2.5 to 3.8 mg/kg/day divided into 2 doses per day
- 30 to 49 mL/min: 2.5 mg/kg once daily or divided into 2 doses per day
- 10 to 29 mL/min: 1.5 mg/kg every 36 hours

Uses

Optimal dosing for colistin is unknown. However, a review of adult data suggest higher colistin concentrations, which may not be achieved with the manufacturer recommended dosing, and a regimen of colistin combined with other antibiotics may be necessary. The safety of higher doses is unknown [7].

Gram-negative infections, multi-drug resistant:
Intermittent IV colistin in combination with at least one other antibiotic, used for the treatment of multi-drug resistant infections, mostly *Acinetobacter baumannii* and *Klebsiella pneumoniae*, resulted in a 76% favorable clinical outcome in a retrospective study (n=21 treatment courses in 18 neonates). Microbiological clearance was documented in 17 of the 21 courses. During therapy with colisin, 5 patients with severe sepsis and multi-organ dysfunction died. The dose of colistimethate sodium ranged from 50,000 to 75,000 IU/kg/day in 3 divided doses [1.7 to 2.5 mg/kg/day of colistin base]. Renal impairment developed in 2 neonates, both subsequently died of multi-organ dysfunction [3].

No significant difference in clinical and microbiological outcomes were observed between very low birthweight infants (VLBW, less than 1500 g) and non-VLBW infants with multi-drug resistant gram-negative bacilli infections treated with colistin 5 mg/kg/day IV in 3 divided doses in a retrospective study (n=66). Efficacy (microbiological clearance and survival) was 89.3% for the VLBW group and 86.8% for the non-VLBW group (p greater than 0.99). Serum magnesium and potassium concentrations were lower (p less than 0.001 for both events), as well as the need for magnesium and potassium supplementation were higher (p less than 0.001 for both events) in the VLBW group compared with non-VLBW group. There was no difference in the rate of acute kidney injury (14.3% vs 2.6%, respectively). *Klebsiella pneumoniae* was the most commonly treated infection, occurring in 60.7% and 63.2% of the VLBW and non-VLBW groups [4].

Aerosolized colistin either as monotherapy [5] or in combination with other IV antibiotics [6] demonstrated potential for treating full-term and pre-term neonates with *Acinetobacter baumannii* (13 of the 16 neonates had multidrug-resistant isolates) ventilator-associated pneumonia in 2 retrospective studies. Neither clinical nor laboratory adverse events were reported. The dosage of colistin base was 4 mg/kg/dose aerosolized with an ultrasonic nebulizer for 15 minutes every 12 hours for a median of 9 days (4 to 14 days) in neonates on a ventilator while receiving concurrent IV antibiotics. All of the 16 neonates who received nebulized colistin cleared the *A baumannii* infection. [6]. Another regimen was colistimethate sodium 1 million international units (33.4 mg colistin base) monotherapy twice daily for an average of 9.1 days (4 to 22 days) [5].

Administration

Intramuscular Route:

Administer by deep IM injection into large muscle mass (eg, gluteal muscles or lateral portion of thigh). The concentration of colistin base is 75 mg/mL [1].

Intravenous Route

Continuous Infusion:

Slowly inject one-half the total daily dose over 3 to 5 minutes at a concentration of 75 mg/mL of colistin base. Add the remaining half of the total daily dose to a compatible solution. Administer by slow IV infusion, starting 1 to 2 hours after the initial dose, over the next 22 to 23 hours. The choice of IV solution and the volume used are dictated by the requirements of fluid and electrolyte management [1].

Intermittent Administration:

Infuse one-half of the total daily dose slowly over 3 to 5 minutes at a concentration of 75 mg/mL colistin base every 12 hours [1]. Doses were added to 5 mL of normal saline and infused over 30 minutes in an observational study of 18 neonates [3].

MEDICATION SAFETY

Contraindications/Precautions

Acute respiratory failure may result when reconstituted colistimethate solution for inhalation is not used promptly. After reconstitution, colistimethate is hydrolyzed to form active components, including polymyxin E1, which has shown to cause localized inflammation of the airway epithelia and eosinophilic infiltration when administered by inhalation [9]
Bronchospasms may occur with inhalation of colistin; consider premedication with a bronchodilator [10][11].
Clostridium difficile-associated diarrhea (CDAD), including mild diarrhea to fatal colitis, has been reported and may occur more than 2 months after administration. If CDAD is suspected or confirmed, discontinue any ongoing antibiotic therapy [1]
Concomitant use of sodium **cephalothin** should be avoided [1]
Increased risk of **neuromuscular blockade** leading to apnea in patients with renal impairment. Dosage adjustment should be reduced in proportion to the extent of the impairment [1]
Respiratory arrest has been reported after IM administration [1]
Reversible and dose-dependent **nephrotoxicity** may occur [1]
Transient **neurological disturbances** (eg, circumoral paresthesia or numbness, tingling or formication of the extremities, generalized pruritus, vertigo, dizziness, and slurring of speech), may occur and dosage adjustments may be necessary [1]

Adverse Effects

The most commonly reported adverse effects are gastrointestinal upset, slurred speech, dizziness, tingling of the extremities or tongue, itching, urticaria, rash, fever, respiratory distress, apnea, and nephrotoxicity [1].
Serum creatinine increased more than 0.5 mg/dL above baseline in 2 out of 18 neonates administered IV colistin [3].
Neither clinical nor laboratory adverse events were reported with **aerosolized** colistin in 8 neonates. Serum creatinine and blood urea nitrogen remained within normal limits 72 hours after completion of colistin therapy [5][6].

Solution Compatibility

NS, D_5NS, D_5 0.45%NS, D_5W

Terminal Injection Site Compatibility

Aminophylline, atropine sulfate, calcium chloride, calcium gluconate, chloramphenicol sodium succinate, chlorothiazide sodium, chlorpheniramine maleate, chlorpromazine hydrochloride, clarithromycin, cloxacillin sodium, cyclophosphamide, dexamethasone sodium phosphate, digoxin, edetate calcium disodium, epinephrine hydrochloride, ergonovine maleate, erythromycin lactobionate, furosemide, gallamine triethiodide, gentamicin sulfate, heparin sodium, hydralazine hydrochloride, hydrocortisone sodium succinate, isoproterenol

hydrochloride, kanamycin sulfate, lidocaine hydrochloride, lincomycin hydrochloride, mechlorethamine hydrochloride, mephentermine sulfate, metaraminol bitartrate, methohexital sodium, methyldopate hydrochloride, nalorphine hydrobromide, norepinephrine bitartrate, oxytocin, penicillin G potassium, penicillin G sodium, phenobarbital sodium, phentolamine mesylate, polymyxin B sulfate, potassium chloride, procainamide hydrochloride, prochlorperazine mesylate, promazine hydrochloride, promethazine hydrochloride, propranolol hydrochloride, streptomycin sulfate, succinylcholine chloride, trimetaphan camsylate, tubocurarine chloride.

Monitoring

Closely monitor for toxicity in pediatric patients [1]. Monitor urine output, BUN, and serum creatinine[8].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Microbiology
Colistimethate sodium is a surface active agent that is used to penetrate and disrupt the cell membrane of bacteria. It has demonstrated bactericidal activity against most strains of aerobic gram-negative microorganisms (*Enterobacter aerogenes, Escherichia coli, Klebsiella pneumonia, and Pseudomonas aeruginosa*) both in vitro and in clinical infections [1].

Pharmacokinetics
Higher serum levels were obtained at 10 minutes following IV administration compared with IM administration [1].
Half-life was 2 to 3 hours after administration (either IM or IV) in both the adult and pediatric populations, including premature infants [1]. The half-life was 2.6 hours in neonates (0 to 7 days) and 2.3 hours in infants 7 days or older [12].
Urine levels ranged, on average, from 270 mcg/mL at 2 hours to 15 mcg/mL at 8 hours following IV administration and 200 mcg/mL to 25 mcg/mL over a similar time period with IM administration [1].

IV Administration Within 6 hours of IV colistin base 5 mg/kg, the colistin concentration was less than 2 mcg/mL in all 7 neonates (median 38 weeks gestation and 13 days postnatal age) after a single IV colistin base dose of 5 mg/kg/day [2].
Nebulization Administration: After a single-dose of ultrasonic-nebulized colistin base 4 mg/kg in 6 neonates (median gestational age 39 weeks (32 to 39) and postnatal age 7 days (3 to 7)) with ventilator-associated pneumonia, 50% of tracheal aspirate concentrations of colistin were below 2 mcg/mL 24 hours after administration. The ratio of colistin plasma concentrations-to-tracheal aspirate was 0.038 (3.8%) [13][14].
The following were the pharmacokinetic parameters for colistin in the tracheal aspirate and plasma via nebulization and in the plasma via IV administration:

Single-Dose, Colistin Pharmacokinetics in Neonates			
Parameters (mean (range))	Nebulization 4 mg/kg (n=6)*		IV 5 mg/kg (n=7)**
	Tracheal Aspirate	Plasma	Plasma
Cmax	24 mcg/mL (15.6 to 34.6 mcg/mL)	0.59 mcg/mL (0.32 to 1.1 mcg/mL)	3 mcg/mL
Tmax	1.8 hours (0.5 to 6 hours)	1.9 hours	1.3 hours
AUC (0 to 24)	147.6 mcg x hr/mL	2.34 mcg x hr/mL	21.1 mcg x hr/mL
AUC (0 to infinity)	183.8 mcg x hr/mL	7.57 mcg x hr/mL	25.3 mcg x hr/mL
Clearance of formed colistin	0.027 L/hr/kg	1.01 L/hr/kg	0.6 L/hr/kg
Half-life	9.8 hours	10.2 hours	9+/-6.5 hours
Vd of formed colistin	0.46 L/kg	11.7 L/kg	7.7+/-9.3 L/kg
KEY: Cmax = maximum colistin concentration, Tmax = time to maximum colistin concentration, AUC = area under the concentration time curve, Vd = apparent volume of distribution			
*Nakwan, 2015 ** Nakwan, 2016			

Pharmacodynamics
The ratio of AUC/MIC of colistin base is the most predictive of antibacterial activity [7].

ABOUT

Special Considerations/Preparation

Each vial containing colistimethate sodium (pentasodium colistin-methanesulfonate) is equivalent to 150 mg of colistin base activity [1]. Colistin base 1 mg is equivalent to 2.4 mg of colistimethate sodium. Colistimethate sodium is 12,500 international units/mg and colistin base is 30,000 international units/mg [15].
Store vials at controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F) [1].

Intravenous:
Reconstitute 150 mg (colistin base) vial with 2 mL sterile water for injection for a resulting concentration of 75 mg/mL colistin base; swirl gently to avoid frothing [1].
Once diluted with sterile water for injection, store solution up to 7 days, between 20 and 25 degrees C (68 and 77 degrees F) or refrigerated between 2 and 8 degrees C (36 and 46 degrees F) [1].
Colistimethate for continuous infusion should be mixed with NS, D5NS, D5W, D5-0.45%NaCl, D5-0.225%NaCl, LR, or 10% invert sugar solution and used within 24 hours [1].

Inhalation: Use immediately after mixed. Do not use after 24 hours. In solution, colistimethate undergoes spontaneous hydrolysis to form its 2 active components polymyxin E1 (colistin A), which is toxic to the lungs, and polymyxin E2 (colistin B). Use after 24 hours can result in increased colistin concentration and the potential for increased lung toxicity [9].

Cosyntropin

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Adrenocortical Insufficiency; Diagnosis
Younger than 2 years: 0.125 mg (0.5 mL) IV or IM (FDA dosage) [1]; alternatively, may use 0.015 mg/kg IV for infants [2].
Low-dose, 0.001 mg (1 mcg) IV may be considered in the setting of short supply [2].
Concomitant medication: Patients receiving corticosteroids such as cortisone or hydrocortisone, or patients receiving spironolactone, should omit pre-test doses of these drugs on test day [3].

Uses

Pediatric FDA Approved Indications
Cosyntropin is indicated, in combination with other diagnostic tests, for use as a diagnostic screening agent for adrenal cortical insufficiency in adults and pediatric patients [1].

Administration

Administer IV or IM [1]

MEDICATION SAFETY

Contraindications/Precautions

Contraindication
History of hypersensitivity to cosyntropin or to any of its excipients [1]

Precautions
Immunologic: Hypersensitivity reactions, including anaphylaxis, have been reported; monitoring recommended [1].
Laboratory abnormalities: Cortisol levels and subsequent diagnosis of adrenocortical insufficiency following administration may be inaccurate if patients are on certain medications because of their effect on cortisol or cortisol binding globulin levels [1].

Adverse Effects

Common: Anaphylactic reaction, bradycardia, tachycardia, hypertension, peripheral edema, and rash [1].

Monitoring

Concurrent use with cortisone, hydrocortisone, spironolactone, or estrogen may alter the test results [3].
Cortisol levels: Measure at baseline and again at exactly 30 and 60 minutes after administration. A post-administration cortisol level of less than 18 mcg/dL at either time point is suggestive of adrenocortical insufficiency [1].

Method Options
Rapid Screening Test (Intramuscular Injection)
Collect blood sample of 6 to 7 mL in a heparinized tube before IM cosyntropin and exactly 30 minutes after IM cosyntropin. Refrigerate blood samples until sent to the laboratory. Determine plasma cortisol response by some appropriate method. If it is not possible to send them to the laboratory or perform the fluorimetric procedure within 12 hours, then the plasma should be separated and refrigerated or frozen until ready to assay [3].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action: Cosyntropin, a synthetic subunit of natural adrenocorticotrophic hormone (ACTH), stimulates adrenal gland to secrete 17-OH corticosteroids, 17-ketosteroids, and/or 17-ketogenic steroids. Extra-adrenal effects include increased melanotropic activity, increased growth hormone secretion and an adipokinetic effect. [3].

ABOUT

Special Considerations/Preparation

Availability: 0.25 mg lyophilized powder for solution [1].
Reconstitution: Add 1 mL of 0.9% sodium chloride for a final concentration of 0.25 mg/mL. Discard any unused solution [1].
Dilution: Diluted cosyntropin in sodium chloride to 5 mcg/mL concentration and stored at

refrigeration (4°C) in both glass and plastic tubes remained approximately 90% potent at 2 months and about 80% potent at 4 months [4].
A diluted (0.5 mcg/mL) cosyntropin solution stored in refrigerator for up to 60 days produced as expected peak 30-minute cortisol responses in healthy adult volunteers (n=49).
Cosyntropin 250 mcg/mL (Synacthen®, Novartis, Manufactured by Alliance Pharmaceutical ltd Chippenham, Wiltshire U.K.) was diluted in 499 mL of 0.9% sodium chloride in a plastic IV fluid container and stored at 2 to 8°C for up to 60 days [5].

Cyclopentolate (Ophthalmic)

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

1 or 2 drops instilled in the eye 10 to 30 minutes prior to funduscopy.
Use solutions containing concentrations of 0.5% or less in neonates.
May be used in conjunction with 1 drop of phenylephrine 2.5% ophthalmic solution.
Apply pressure to the lacrimal sac during and for 2 minutes after instillation to minimize systemic absorption.

Uses

Induction of mydriasis and cycloplegia for diagnostic and therapeutic ophthalmic procedures.

MEDICATION SAFETY

Adverse Effects

Feedings should be withheld for 4 hours following procedure. Systemic effects are those of anticholinergic drugs: Fever, tachycardia, vasodilatation, dry mouth, restlessness, delayed gastric emptying and decreased gastrointestinal motility, and urinary retention. The use of solutions with concentrations of 1% or greater have caused systemic toxicity in infants.

Monitoring

Monitor heart rate and assess for signs of ileus prior to feeding.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Anticholinergic drug that produces pupillary dilation by inhibiting the sphincter pupillae muscle, and paralysis of accommodation. Maximal mydriasis occurs 30 to 60 minutes

following administration. Recovery of accommodation occurs in 6 to 24 hours. Without lacrimal sac occlusion, approximately 80% of each drop may pass through the nasolacrimal system and be available for rapid systemic absorption by the nasal mucosa.

ABOUT

Special Considerations/Preparation

Supplied as ophthalmic solution 0.5% in 15-mL Drop-tainers, and 1% and 2% concentrations in 2-, 5- and 15-mL Drop-tainers. Store away from heat. **Do not refrigerate.** A preparation containing cyclopentolate 0.2% and phenylephrine 1% (Cyclomydril®) is commercially available in 2- and 5-mL Drop-tainers.
A combination eye drop solution ("Caputo drops") may be prepared in a 15-mL bottle with 3.75 mL of cyclopentolate 2%, 7.5 mL of tropicamide 1%, and 3.75 mL of phenylephrine 10%. The final solution contains cyclopentolate 0.5%, tropicamide 0.5%, and phenylephrine 2.5%.

Dexamethasone

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Facilitation of Extubation
DART trial protocol: 0.075 mg/kg/dose every 12 hours for 3 days, 0.05 mg/kg/dose every 12 hours for 3 days, 0.025 mg/kg/dose every 12 hours for 2 days, and 0.01 mg/kg/dose every 12 hours for 2 days [1]. Doses may be administered IV slow push or orally.

Inflammatory ophthalmic conditions: Instill 1 to 2 drops topically in the conjunctival sac(s) every hour for severe disease or up to 4 to 6 times daily for mild disease. In severe disease, taper the dose and then discontinue as the inflammation resolves [2].

Uses

Chronic Lung Disease (CLD) - AAP Guidelines
• High dose postnatal corticosteroids (PCS) are not recommended to prevent or treat CLD in preterm infants [14].
• Routine use of PCS is currently not recommended by the American Academy of Pediatrics. However, the decision to use corticosteroids to prevent or treat CLD should be individualized to each patient and discussed with the parents [14].
• If PCS is given, a low dose given for a short, predetermined duration (eg, extubation) is recommended. If an infant does not show clinical response to PCS within 72 hours, continued treatment is not recommended [14].
• Dexamethasone and hydrocortisone are the most studied and used PCS for treating infants with CLD. Inhaled corticosteroids do not appear to offer any advantages to systemic corticosteroids [14].
• Indomethacin should not be used concurrently with PCSs [14].

Low-dose dexamethasone has been used successfully to **facilitate extubation and improve lung function** acutely in preterm infants at high risk for developing chronic lung disease. Low doses have not been associated with substantial effects with regard to mortality or development of bronchopulmonary dysplasia (BPD) at 36 weeks [15][1][16]. High-dose dexamethasone (eg, 0.5 mg/kg/day) has been associated with a reduction in the incidence of BPD, but also an increased risk for short-term adverse effects (hyperglycemia, hypertension, gastrointestinal perforation, infection risk) and adverse long-term neurodevelopmental outcomes (cerebral palsy (CP)) [15][17][18]. A review of meta-analyses looking at the timing and dosage of postnatal steroids found the development of CP was associated with early steroid use (first week of life) in patients at lower risk for BPD [15]. A prospective cohort study found that higher steroid exposure was associated with an increased risk for CP [19].. A shorter course, 7 days, compared with a longer course, 10 days, of dexamethasone for bronchopulmonary dysplasia was as effective in facilitating extubation (56% vs 67%,

p=0.42) within 14 days of starting dexamethasone in mechanically-ventilated preterm infants (less than 29 weeks' gestational age) in a retrospective study (n=59). Mean postnatal age was 36 days and 33 days for the infants treated for 7 days and 10 days, respectively. The total dose for the 7-day regimen was 0.72 mg/kg (0.075 mg/kg/dose every 12 hours for 3 days, 0.05 mg/kg/dose every 12 hours for 2 days, 0.025 mg/kg/dose every 12 hours for 1 day, and 0.01 mg/kg/dose every 12 hours for 1 day). The total dose for the 10-day regimen was 0.89 mg/kg [20].

Anthrax, adjunct: Although data are lacking, consider adjunctive corticosteroids for the treatment of severe cerebral edema or meningoencephalitis [21].

Pediatric FDA Approved Indications

Ophthalmic

Indicated in pediatric patients of all ages for steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe such as allergic conjunctivitis, acne rosacea, superficial punctate keratitis, herpes zoster keratitis, iritis, cyclitis, selected infective conjunctivitides when inherent hazard of steroid use is accepted to obtain an advisable diminution in edema and inflammation; corneal injury from chemical, radiation, or thermal burns, or penetration of foreign bodies [2].

Systemic

Use as an immunosuppressant and in a variety of antiinflammatory disorders to reduce edema (eg, due to tumors, infection) and to lessen the effects of neurologic disorders based on adult studies. For the treatment of nephrotic syndrome, dexamethasone is approved in patients older than 2 years of age, and for the palliative management of aggressive lymphomas and leukemias, it is approved in patients 29 days and older. Due to its lack of mineralocorticoid effects, dexamethasone is not indicated as replacement therapy for patients with adrenal insufficiency [7][8][6][22].

Administration

Intravenous: Can be administered undiluted or can be diluted to a concentration of 0.1 to 1 mg/mL in NS for intravenous infusion [3][4][5][6].

Ophthalmic: Shake well before use [2].

Oral: Take large doses with meals and take antacids between meals to prevent peptic ulcer. Mix the concentrate solution with liquid or semi-solid food such as water, juices, soda, applesauce or puddings and consume immediately; do not store for future use [7][8].
The IV formulation of dexamethasone has been used orally in pediatric patients [9], including a one-time dose for asthma exacerbation in a retrospective study. Injectable dexamethasone was mixed with a small amount of juice [10]. Stability data are available [11][12]; however, there are no bioequivalence data in pediatric patients [13].

MEDICATION SAFETY

Contraindications/Precautions

CONTRAINDICATIONS
Systemic Use: Contraindicated in patients with systemic fungal infection [7][8].
Ophthalmic Use: Contraindicated in acute, untreated bacterial infections; mycobacterial ocular infections; epithelial herpes simplex (dendritic keratitis); vaccinia, varicella, and most other viral diseases of the cornea and conjunctiva; fungal disease of ocular structures; and in those persons who have shown hypersensitivity to any component of this preparation [2].

PRECAUTIONS
Systemic Use
Administration: Injecting corticosteroids into the epidural space of the spine may result in rare but serious neurologic problems (ie, spinal cord infarction, loss of vision, stroke, seizure, paralysis, or death) [23].
Immunologic: Contains bisulfate, a sulfite that can cause anaphylactic allergic-type reactions seen more frequently in asthmatic patients [7][8].
Ophthalmic: Use of corticosteroid-containing product for more than 6 weeks or development of ocular symptoms; consider ophthalmologist referral [24]
Ophthalmic Use
Ophthalmic: Prolonged use may result in ocular hypertension and/or glaucoma, with damage to the optic nerve, defects in visual acuity and fields of vision, and posterior subcapsular formation; monitoring recommended during long-term (10 day or longer) therapy [2]
Ophthalmic: Prolonged use may increase the risk of secondary ocular infections due to reduced host response [2]
Ophthalmic: Prolonged use may result in persistent fungal infection of the cornea [2]
Ophthalmic: Perforations may occur in patients receiving topical corticosteroids in diseases known to cause thinning of the cornea or sclera [2]
Ophthalmic: Corticosteroids may mask infection or enhance existing infection in the presence of acute purulent conditions or parasitic infections of the eye [2].

Adverse Effects

The February 2002 AAP and CPS statement strongly discourages routine use of dexamethasone. If dexamethasone is used for CLD risk reduction, 1) Treat only those infants at highest risk; 2) Use lower than traditional pharmacologic doses; 3) Begin treatment after Day 7 but before Day 14 of life; 4) Do not give concurrently with indomethacin; 5) Use preservative-free drug wherever possible.
The DART trial found no association with long-term morbidity, but other studies have reported an increased risk of cerebral palsy. Most evidence suggests no increase in the incidence of ROP or the need for cryotherapy. Gastrointestinal perforation and GI hemorrhage occur more frequently in patients treated beginning on Day 1 and in those also being treated concurrently with indomethacin. Hyperglycemia and glycosuria occur frequently after the first few doses, and one case of diabetic ketoacidosis has been reported. Blood pressure increases are common, and hypertension occurs occasionally. Cardiac effects noted by Day 14 of therapy include increased left ventricular wall thickness with outflow tract obstruction and transient impairment of left ventricular filling, systolic anterior motion of the

mitral valve, and ST-segment depression. Other potential short-term adverse effects include sodium and water retention, hypokalemia, hypocalcemia, hypertriglyceridemia, increased risk of sepsis, renal stones (in patients receiving furosemide), osteopenia, and inhibition of growth. Adrenal insufficiency may occur secondary to pituitary suppression.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Acyclovir, amikacin, aminophylline, aztreonam, caffeine citrate, cefepime, cimetidine, famotidine, fentanyl, fluconazole, furosemide, heparin, hydrocortisone succinate, lidocaine, linezolid, lorazepam, meropenem, methadone, metoclopramide, milrinone, morphine, nafcillin, netilmicin, piperacillin/tazobactam, potassium chloride, propofol, ranitidine, remifentanil, sodium bicarbonate, and zidovudine.

Terminal Injection Site Incompatibility

Glycopyrrolate, midazolam, and vancomycin.

Monitoring

Systemic Use:
Assess for hyperglycemia and hyperlipidemia. Monitor blood pressure. Guaiac gastric aspirates. Echocardiogram if treating longer than 7 days.

Ophthalmic use: Monitor intraocular pressure during long-term (10 day or longer) therapy [2]
Periodic slit-lamp microscopy is required in the treatment of herpes simplex [2]

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Stabilizes lysosomal and cell membranes, inhibits complement-induced granulocyte

aggregation, improves integrity of alveolar-capillary barrier, inhibits prostaglandin and leukotriene production, rightward shifts oxygen-hemoglobin dissociation curve, increases surfactant production, decreases pulmonary edema, relaxes bronchospasm. Hyperglycemia is caused by inhibition of glucose uptake into cells and decreased glucokinase activity. Increased triglyceride synthesis is due to hyperinsulinemia and increased acetyl-CoA carboxylase activity. Blood pressure is increased due to increased responsiveness to endogenous catecholamines. Increases protein catabolism with potential loss of muscle tissue, increases urinary calcium excretion because of bone resorption, and suppresses pituitary ACTH secretion. Biologic half-life is 36 to 54 hours.

ABOUT

Special Considerations/Preparation

Injection
Availability: Dexamethasone sodium phosphate for injection is available in concentrations of 4 mg/mL (benzyl alcohol preservative 10 mg/mL) and 10 mg/mL (preservative free or benzyl alcohol preservative 10 mg/mL).
Stability: Stable for 30 days under refrigeration at dilutions of 0.2 mg/mL and 0.4 mg/mL in NS in PVC minibags [5]. Stable for 22 days at room temperature at dilutions of 0.1 mg/mL and 1 mg/mL in NS in polypropylene syringes [3]. Stable for 28 days under refrigeration and at room temperature at a dilution of 1 mg/mL in bacteriostatic NS in glass vials [4]. Stable for up to 14 days at room temperature at dilutions of 0.08 mg/mL and 0.6 mg/mL in D_5W in polyvinyl chloride bags [25].

Ophthalmic
Availability: Dexamethasone 0.1% ophthalmic suspension [2]

Oral
Availability:[7][8]

- **Oral solution** 0.5-mg/5 mL (0.1-mg/mL) and 1-mg/mL (Intensol™ concentrate). Intensol™ concentrate contains alcohol 30%. Discard opened bottle of Intensol™ after 90 days.
- **Tablets** 0.5-, 0.75-, 1-, 1.5-, 2-, 4-, and 6-mg strengths.

Extemporaneous Oral Suspension
0.5 mg/mL oral suspension: Dilute 1 mL of the 4 mg/mL IV solution up to a total volume of 8 mL with a 1:1 mixture of Ora-Sweet® and Ora-Plus®. The oral suspension was physically and chemically stable for up to 91 days with or without refrigeration [11].
1 mg/mL oral suspension: Dilute dexamethasone 4 mg/mL solution for injection with either Oral Mix or Oral Mix SF to make 1 mg/mL oral suspension. The oral suspension was stable for up to 91 days when stored in amber glass, plastic bottles, or plastic syringes at 25 degrees C or in amber glass bottles or plastic bottles at 4 degrees C [12].

DOSING/ADMINISTRATION

Dose

Hypoglycemia
IV
Initial Dose: 0.2 g/kg IV (2 mL/kg) as $D_{10}W$ [1][2].
Maintenance Dose: Continuous infusion of a 5% to 10% dextrose IV solution with appropriate maintenance electrolytes at an initial glucose infusion rate of 5 to 8 mg/kg/minute. Titrate rate to attain normoglycemia [1][2]. Higher doses may be necessary (10 to 20 mg/kg/minute) to maintain acceptable blood glucose levels, particularly in patients with persistent hyperinsulinemic hypoglycemia. Abruptly discontinuing a dextrose infusion is not recommended due the risk for rebound hypoglycemia [3].
Buccal
48 hours or younger (35 weeks gestation or more): 200 mg/kg of dextrose gel (40%) massaged into the buccal mucosa, may be repeated up to 6 doses over 48 hours [4].

Hyperkalemia
Initial, continuous IV infusion of 0.5 g/kg/hour dextrose and 0.1 to 0.2 units/kg/hour regular insulin. Dextrose and insulin dosages are adjusted based on serum glucose and potassium concentrations.

Parenteral Nutrition Recommendations
An initial dextrose infusion rate of 6 to 8 mg/kg/minute, advanced as tolerated to a goal rate of 10 to 12 mg/kg/minute, is recommended in neonates. An initial rate of 4 to 8 mg/kg/minute should be considered in preterm neonates.

Uses

Hyperkalemia in combination with insulin

Hypoglycemia, Prophylaxis: The incidence of hypoglycemia was reduced with prophylactic dextrose buccal gel compared with placebo in babies at 1 hour of age at risk of developing neonatal hypoglycemia in a randomized, double-blind, placebo-controlled, dose-finding study (n=416); relative risk was 0.68 (95% CI, 0.47 to 0.99) for the 200 mg/kg single dose. There was no difference between any dextrose dose and placebo in the rate of intensive care admission, breast feeding rates, and supplementary dextrose. The majority of babies (73%) were born to mothers with diabetes [5].

Hypoglycemia, Treatment: Administration of buccal dextrose gel (40%) improved blood glucose better than feedings alone in at-risk late preterm and term babies who became hypoglycemic within the first 48 hours of birth in a randomized, double-blind, placebo-

controlled study (n=237). Treatment failure rates were 14% and 24% (relative risk, 0.57 (95% CI, 0.33 to 0.98)) for the dextrose and placebo groups, respectively. Rebound and recurrent hypoglycemia were no different between dextrose gel and placebo groups. Almost all babies were breastfed [4]. No additional risks or benefits were identified in 184 out the 237 eligible infants evaluated at 2 years' corrected age. There was no difference between dextrose gel and placebo in neurosensory impairment or processing difficulties [6].
Dextrose IV is recommended for hypoglycemia in the setting of cardiopulmonary resuscitation [7][8].

Nutritional supplement in parenteral nutrition solutions

Administration

IV: Generally, glucose concentrations greater than 15% should be administered via a central vein to minimize risk of phlebitis and thrombosis. However, in one study in term neonates (n=121), peripheral infusion of a 20% glucose solution did not cause a higher rate or severity of phlebitis compared with peripheral infusion of a 15% glucose solution. Bolus doses should be administered only by slow IV injection. Abruptly discontinuing a dextrose infusion is not recommended due the risk for rebound hypoglycemia.
For Hypoglycemia, use continuous infusion of a 5% to 10% dextrose IV solution with appropriate maintenance electrolytes [1][2].
Buccal: Prior to application, dry the mouth with a gauze [4]. Massage the gel into the buccal mucosa [5][4] followed by breastfeeding [5].

MEDICATION SAFETY

Contraindications/Precautions

Contraindicated when intracranial or intraspinal hemorrhage is present. Concentrated dextrose solutions (ie, 25% and 50%) are hypertonic and may cause phlebitis and thrombosis at injection site. Rapid administration may cause significant hyperglycemia and possible hyperosmolar syndrome.

Adverse Effects

Excessive glucose provided by parenteral nutrition is associated with promotion of fat deposition, liver impairment and steatosis, and impairment of protein metabolism [11].

Solution Compatibility

Most standard IV solutions.

Terminal Injection Site Compatibility

Most drugs.

Terminal Injection Site Incompatibility

Caspofungin, erythromycin, phenytoin, and procainamide.

Monitoring

Therapeutic and Toxic Laboratory Monitoring
Perform periodic laboratory determinations to monitor for changes in electrolyte concentrations and acid-base balance, especially during prolonged parenteral therapy or when clinically warranted [9]
Monitor blood and urine glucose [9]
Hyperkalemia: Monitor ECG changes and serum glucose during therapy [10].

Therapeutic and Toxic Physical Monitoring
Monitor for changes in fluid balance periodically during prolonged parenteral therapy or when clinically warranted [9].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Dextrose restores blood glucose levels in hypoglycemia and provides a source of carbohydrate calories. Intravenous dextrose provides 3.4 kcal/g [12]. When combined with insulin for the treatment of hyperkalemia, dextrose stimulates the sodium-potassium (Na-K) adenosine triphosphatase pump (ATP) leading to an intracellular shift of potassium.

ABOUT

Special Considerations/Preparation

Injection

Available: 50% concentrated solution in 50-mL single-dose vials and syringes, and 25% concentrated solution in single-use 10-mL syringes. Also available in various other concentrations in large-volume IV solutions.

Oral

Available: Dextrose gel

•Dex4® contains d-glucose 15 g/33 g pouch

•Glutose 15 gel™ contains d-glucose (dextrose) 15 g/37.5 g (40%) [13].

•SugarUp™ 40% glucose gel contains 40% glucose in a 15-mL cup (http://www.sandboxmedical.com/PDF/5-17021-004-SugarBabies-40-Glucose-Datasheet.pdf).

Diazoxide

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Hypoglycemia due to Hyperinsulinism
Initial: 10 mg/kg/day orally divided every 8 hours [1].
Usual Maintenance: 8 to 15 mg/kg/day orally in equally divided doses every 8 to 12 hours [1].
Adjust doses to achieve desired clinical and laboratory effects. If not effective within 2 to 3 weeks, then discontinue [1].

Dose Adjustments
Renal Impairment: No specific dose adjustment recommendations are available for neonates, but a reduced dosage should be considered in patients with renal impairment [1].

Uses

Hypoglycemia due to Hyperinsulinism: In small for gestational age infants with hyperinsulinemic hypoglycemia during the first 5 days of life, serum glucose concentration normalized sooner with oral diazoxide compared with placebo, in a randomized, double-blind study (N=30). The median time to achieve hypoglycemia control (defined as glucose IV infusion of 4 mg/kg/min or less for a minimum of 6 hours) was 40 hours for the diazoxide group and 72 hours (p = 0.01) for the placebo group. The total duration of intravenous fluids (114 vs 164 hours; p=0.004) and time to achieve euglycemia (30 vs 60 hours, p = 0.001 or less) was less with diazoxide compared with placebo. Diazoxide dosage was 3 mg/kg/dose orally every 8 hours and increased to 4 mg/kg/dose every 8 hours if hypoglycemia persisted after 48 hours; subsequently tapered by 1 mg/kg/dose every 72 hours once the infant was euglycemic for at least 72 hours [2]

Pediatric FDA Approved Indications
Treatment of hypoglycemia due to hyperinsulinism associated with the following conditions: leucine sensitivity, islet cell hyperplasia, nesidioblastosis, extrapancreatic malignancy, islet cell adenoma, or adenomatosis. May also be used preoperatively and postoperatively, as a temporary measure for persistent hypoglycemia [1].

Administration

Shake suspension well before administration [1].

MEDICATION SAFETY

Contraindications/Precautions

Contraindications
•Functional hypoglycemia [1]
•Hypersensitivity to diazoxide or to other thiazides [1]

Precautions
Cardiovascular: Fluid retention from diazoxide may result in congestive heart failure for those with compromised cardiac reserve; diuretics may be used [1].
Cardiovascular: Antihypertensive effects may be enhanced when diazoxide is coadministered with antihypertensive agents [1].
Concomitant Use: Thiazides may potentiate the hyperglycemic and hyperuricemic actions of diazoxide [1].
Endocrine and Metabolic: Ketoacidosis and nonketotic hyperosmolar coma have been reported, usually during intercurrent illness and at recommended doses; monitoring required [1].
Endocrine and Metabolic: Hyperuricemia or history of gout; monitoring required [1].
Hepatic: Newborns with bilirubinemia; bilirubin may be displaced from albumin by diazoxide [1].
Musculoskeletal: Abnormal facial features developed in 4 children treated for more than 4 years with diazoxide [1]..
Ophthalmic: Cataracts (transient) have occurred in association with hyperosmolar coma in an infant; resolved with correction of hyper-osmolarity [1].
Pharmacokinetics: Oral suspension may result in higher blood concentrations than oral capsules; dosage adjustment may be necessary when switching between formulations [1].
Renal: Renal function, impaired; risk of drug toxicity [1].
Respiratory: Pulmonary hypertension has been reported in infants and newborns administered diazoxide [1] for treatment of low blood sugar and may occur within days or a few months of administration. Risk factors for pulmonary hypertension are those with meconium aspiration syndrome, respiratory distress syndrome, transient tachypnea, pneumonia, sepsis, congenital diaphragmatic hernia, or congenital heart disease. Symptoms may include difficulty breathing, flared nostrils, grunting, chest wall retractions, rapid breathing, difficulty feeding, bluish color of the lips or skin [3]. Discontinue use if pulmonary hypertension develops . Symptoms may be reversible upon discontinuation [1].

Adverse Effects

Hirsutism and hypertrichosis have been reported commonly in children. Hypotension, chest pain, thrombocytopenia, and neutropenia have been reported rarely [4][5][6][7][8]. Concurrent treatment with a thiazide diuretic is recommended to prevent associated fluid retention from diazoxide [9][10][7][8].

Monitoring

Laboratory Parameters
•Careful monitoring of blood glucose concentrations is recommended during therapy, particularly during treatment initiation and until stabilization. Monitoring urine for sugar and ketones is recommended for patients under stress. A dose reduction may be required in patients with hyperglycemia or glucosuria [1].
•Evaluate serum electrolyte levels in patients with impaired renal function [1].
•Monitor BUN and creatinine clearance [1]
•Monitor hematocrit, platelet counts, and leukocytes (total and differential) [1].
•Monitor AST and serum uric acid level [1].
Physical Exam
•Monitor for respiratory distress, especially in patients with risk factors for pulmonary hypertension [1].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action: Diazoxide is a nondiuretic benzothiadiazine derivative, and when given orally induces a quick elevation in blood glucose level through inhibition of insulin release from the pancreas, and also due to an extrapancreatic effect. It also decreases sodium and water excretion, leading to fluid retention, which may be severe. May also cause increased heart rate and elevated serum uric acid levels [5].

Onset: Hyperglycemia begins within an hour and lasts no more than 8 hours in normal patients.
Protein binding: Highly protein bound (more than 90%).
Elimination: Primarily in the kidneys.
Half-life: In children (4 months to 6 years of age) on long-term therapy, plasma half-life after oral administration was 9.5 to 24 hours. Half-life is increased in patients with renal impairment [5].

ABOUT

Special Considerations/Preparation

Availability: Proglycem® 50 mg oral capsules and oral suspension 50 mg/mL. Alcohol content is 7.25%. Protect from light. Store at room temperature [1].

Extemporaneous Suspension 10 mg/mL[11]

- **Bulk diazoxide powder**
- Weigh bulk diazoxide powder (2 g)
- Mix with mortar in glycerine (3 mL) until forming a smooth paste
- Add enough Oral Mix or Oral Mix SF incrementally to form a uniform suspension and to bring the total volume to 200 mL
- Stable for 90 days at 5°C (refrigeration) and 25°C (room temperature) and stored in amber plastic oral syringes or amber PET bottles
- **Diazoxide capsules**
- Pulverize the contents of 25 diazoxide 100 mg capsules using a pestle in a mortar
- Mix with small amounts of Oral Mix or Oral Mix SF (10 mL) to form a homogenous paste
- Add Oral Mix or Oral Mix SF in small increments to bring the required total volume (250 mL)
- Thoroughly mix to form a uniform suspension
- Stable for 90 days at 5°C (refrigeration) and 25°C (room temperature) and stored in amber plastic oral syringes or amber PET bottles

Didanosine

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

HIV Infection

14 days or older: 100 mg/m^2 orally twice daily (manufacturer dose) [1]; 50 mg/m^2 twice daily may be more appropriate for neonates (guideline dose) [2].

Uses

HIV-1 infection

Younger than 15 days: Data are insufficient to make a general recommendation for complete combination antiretroviral therapy (cART) in preterm or term infants younger than 15 days (until 42 weeks' postmenstrual age). Consult a pediatric HIV expert if considering a 3-drug antiretroviral (ARV) regimen in infants younger than 2 weeks or premature infants. The preferred *initial* regimen is 2 NRTIs (zidovudine plus either (lamiVUDine or emtricitabine)) plus nevirapine. There are no data demonstrating improved outcomes when starting treatment within the first 14 days of age compared with after 14 days of age [2].

14 days or older and 42 weeks' post-gestational age: The preferred *initial* regimen is 2 NRTIs (zidovudine plus (lamiVUDine or emtricitabine)) plus lopinavir/ritonavir-boosted. If the infant is on nevirapine considering changing to lopinavir/ritonavir-boosted [2].

Pediatric FDA Approved Indications

Treatment of HIV-1 infection, in combination with other antiretroviral agents, in children 2 weeks or older [1].

Administration

Preferably, administer on an empty stomach (30 minutes before or 2 hours after a feeding). Shake well before measuring dose [1].

MEDICATION SAFETY

Contraindications/Precautions

CONTRAINDICATIONS

Contraindicated with the coadministration of allopurinol, ribavirin, or stavudine [3][5].

PRECAUTIONS
Concomitant use: Avoid use with hydroxyurea [4][3] (with or without stavudine) [6]
Endocrine and metabolic: Lipoatrophy has been reported predominately in the face, limbs, and buttocks; severity related to cumulative exposure and is often not reversible. Monitoring recommended and consider alternative regimen if there is a suspicion of lipoatrophy [4][3]
Hepatic: Severe hepatomegaly with steatosis, including fatalities, have been reported with nucleoside analogs; increased risk in obesity, female gender, prolonged nucleoside exposure, or known risk factors for liver disease; suspend treatment if signs or symptoms occur [4][3][7].
Hepatic: Patients with preexisting liver dysfunction, including chronic active hepatitis, have increased risk of severe and potentially fatal hepatic adverse events; monitoring recommended and interruption or discontinuation of therapy may be necessary [7][6].
Hepatic: Non-cirrhotic portal hypertension has been reported, including fatalities or cases requiring liver transplantation; onset occurred months to years after start of therapy; discontinue use if suspected[7][6].
Immunologic: Autoimmune disorders (eg, Graves' disease, polymyositis, Guillain-Barré syndrome) have been reported; onset variable, may occur many months after treatment initiation [7][6].
Immunologic: Immune reconstitution syndrome has been reported including inflammatory response to indolent or residual opportunistic infections; occurs during initial treatment phase[7][6].
Neurologic: Peripheral neuropathy has been reported; increased risk in patients with advanced HIV disease, history of neuropathy, or concurrent neurotoxic drug therapy; discontinuation may be necessary [7][6].
Ophthalmic: Retinal changes and optic neuritis have been reported; monitoring recommended [7][6].

Adverse Effects

Pancreatitis occurred in 3% (2 out of 60) of pediatric patients during a clinical trial at doses below 300 mg/m(2)/day [1]. Common adverse events include diarrhea, abdominal pain, vomiting, rash, and increased liver enzymes [1]. Peripheral neuropathy, non-cirrhotic portal hypertension, retinal changes, optic neuritis, and insulin resistance/diabetes mellitus have also been reported in pediatric patients [2].

Black Box Warning

Warning: Pancreatitis, Lactic Acidosis and Hepatomegaly with Steatosis [3][4]

- Fatal and nonfatal pancreatitis has occurred during therapy with didanosine used alone or in combination regimens in both treatment-naive and treatment-experienced patients, regardless of degree of immunosuppression. Didanosine should be suspended in patients with suspected pancreatitis and discontinued in patients with confirmed

pancreatitis.

- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including didanosine and other antiretrovirals. Fatal lactic acidosis has been reported in pregnant women who received the combination of didanosine and stavudine with other antiretroviral agents. Coadministration of didanosine and stavudine is contraindicated because of increased risk of serious and/or life-threatening events. Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occurs.

Monitoring

[2]

Antiretroviral Monitoring in Children (adjust schedule based on the specific antiretroviral regimen)							
	Entry into Care†	ART Initiation ††	1 to 2 weeks after initiation	2 to 4 weeks after initiation	Every 3 to 4 months †††	Every 6 to 12 months ‡	Virologic Failure (Prior to switching ARV regimen)
		If clinical, immunologic, or virologic deterioration is suspected, perform more frequent CD4 cell count and plasma viral load monitoring. If toxicity noted, perform testing more frequently until toxicity resolved					
Medical History and Physical Examination ‡‡, ‡‡‡	X	X	X	X	X		X
Adherence Evaluation ‡‡‡		X	X	X	X		X
CBC with differential †††	X	X		X	X		X
Chemistries †††, ♦♦	X	X		X	X		X
Lipid Panel ‡	X	X				X	
Random Plasma Glucose ♦♦♦		X				X	
Urinalysis	X	X				X	
CD4 count	X	X			X		X

Plasma Viral Load ♦	X	X		X	X		X
Resistance Testing	X						X
Hepatitis B screening ¶	X						X
Pregnancy Test for Girls and Young Women of Childbearing Potential	X	X					X
HLA-B*5701 ¶¶	X						

KEY: ARV = Antiretroviral; ART = Antiretroviral therapy; CBC = complete blood count

† If a child does not initiate ART after receiving an HIV diagnosis, the child's CD4 count and plasma viral load should be monitored at least every 3 to 4 months.

†† If ART is initiated within 30 to 90 days of a pre-therapy laboratory result, repeat testing may not be necessary.

††† CD4 cell count, CBC, and chemistries can be monitored less frequently (every 6 to 12 months) in children and youth who are adherent to therapy and have CD4 cell count values well above the threshold for opportunistic infection risk, have sustained viral suppression, and have stable clinical status for more than 2 to 3 years. Viral load testing every 3 to 4 months is generally recommended to monitor ARV adherence.

‡ If lipids have been abnormal in the past, more frequent monitoring might be needed. For patients treated with TDF, more frequent urinalysis should be considered.

‡‡ Pay special attention to changes in weight that might occur after altering an ARV regimen. Weight gain or weight loss may occur when using some ARV drugs.

‡‡‡ Virtual visits may be appropriate at some times points, particularly for adherence assessments and for visits for established patients.

♦ Some experts monitor viral load more often (with each injection) in adolescents initiating injectable cabotegravir and rilpivirine (CAB and RPV). Viral load monitoring should be performed 4 to 8 weeks after switching to long-acting CAB and RPV. HIV-RNA also should be checked in patients with unplanned missed visits and delayed dosing of long-acting CAB and RPV. When viremia develops during long-acting therapy, resistance testing, including integrase resistance testing, should be performed. Follow-up dosing in patients with missed doses should not be delayed while waiting for viral load and resistance test results. However, regimen changes should be prompted if resistance to CAB and/or RPV is discovered.

♦♦ Refers to a comprehensive metabolic panel. Some experts perform a comprehensive panel at entry and routinely test Cr, ALT, AST, with additional tests tailored to the history of the individual patient

♦♦♦ Random plasma glucose is collected in gray-top blood collection

tube or other designated tube. Some experts would consider monitoring HgbA1C, rather than blood glucose, in children at risk for prediabetes/diabetes. ¶ Only recommended for individuals who have previously demonstrated no immunity to HBV and who are initiating a regimen that contains ARV drugs with activity against HBV (ie, lamivudine, emtricitabine, tenofovir alafenamide, or tenofovir disoproxil fumarate). ¶¶ Conduct HLA-B*5701 on entry prior to initiating abacavir if not done previously. Choose an alternative ARV drug if the patient is HLA-B*5701 positive.
Reference: https://clinicalinfo.hiv.gov/en/guidelines/pediatric-arv/whats-new April 2023

Monitor for early signs and symptoms of portal hypertension (eg, thrombocytopenia and splenomegaly). Perform retinal examinations periodically to screen for retinal changes and optic neuritis [1].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action: Didanosine is a nucleoside reverse transcriptase inhibitor active against HIV type 1 [1].

Absorption: The AUC is equivalent for buffered or enteric-coated formulations. Mean bioavailability is approximately 25% in children. Cmax occurs from 0.25 to 1.5 hours following oral administration of the pediatric powder for solution. Food decreases absorption [1].
Distribution: Protein binding is less than 5% [1].
Excretion: Primarily eliminated renally (50%) [1].
Clearance: A population pharmacokinetic analysis from 9 clinical trials in 106 pediatric (neonate to 18 years of age) showed that body weight is the primary factor associated with oral clearance. Clearance was not affected by dosing schedule (once vs twice daily) or formulation (powder for oral solution, tablet, and delayed-release capsule) [1].
Half-life: Mean elimination half-life in children (8 months or older) is 0.8 hours [1].

ABOUT

Special Considerations/Preparation

Availability: Pediatric powder for oral solution in 4- and 8-ounce glass bottles containing 2 g and 4 g of didanosine, respectively.
Reconstitute each 2-g or 4-g bottle with 100 mL or 200 mL of purified water, USP,

respectively, for an initial concentration of 20 mg/mL. This solution should be immediately mixed with one part Maximum Strength Mylanta® Liquid, resulting in a final concentration of didanosine 10 mg/mL. Shake well before use. Refrigerate admixture at 2 to 8 degrees C (36 to 46 degrees F) for up to 30 days, and discard any unused portion after this time [1].

Digoxin Immune Fab (Ovine)

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Digoxin Toxicity
There are limited safety data in neonatal patients. Dosing estimates are based on calculations derived for adult dosing [1].
Each vial of digoxin immune Fab (40 mg purified digoxin-specific Fab fragments) will bind approximately 0.5 mg of digoxin or digitoxin [1].

Acute Ingestion of Known Amount
Dose (in vials) = (digoxin ingested (mg) X bioavailability)/0.5 mg of digitalis bound per vial [1](bioavailability of digoxin solution = 0.85 [2]; bioavailability of digoxin tablets = 0.8). If in any case, the dose estimated based on ingested amount differs considerably from that calculated based on the serum digoxin, it may be preferable to use the higher dose estimate [1].

Chronic Digoxin Toxicity
Unknown digoxin level: single vial (40 mg) IV initially [1].
Known digoxin level: dose in mg = 40 mg x (serum digoxin concentration in nanogram (ng)/mL x weight in kg)/100 [1].

If toxicity has not adequately reversed after several hours, or appears to recur, readministration of digoxin immune Fab may be required [1].

Uses

Digoxin and related cardiac glycosides toxicity: Cardiac glycoside poisoning can be caused by medications (digoxin and digitoxin), plants (foxglove and yellow oleander), and certain toad venoms (ingested as ethnopharmaceuticals or hallucinogens). Administration of digoxin immune Fab can reverse life-threatening dysrhythmias from digoxin poisoning, with a 50% to 90% response rate reported within 30 to 45 minutes. Administration of digoxin immune Fab is recommended for digoxin or digitoxin poisoning and is reasonable to administer for poisoning due to Bufo toad venom and yellow oleander. Use of digoxin immune Fab in poisoning from other cardiac glycosides may be reasonable, but have limited supporting data [3].

Pediatric FDA Approved Indications
Digoxin immune Fab is indicated for life-threatening or potentially life-threatening digoxin toxicity or overdose in children, including the following situations: ingestion of fatal doses of 4 mg (or 0.1 mg/kg) or more, or amounts leading to serum concentrations of 10 ng/mL or greater; chronic ingestions leading to levels greater than 4 ng/mL; and in the presence of

severe ventricular arrhythmias, bradycardia, second/third degree heart block that is unresponsive to atropine, or potassium levels greater than 6 mEq/L with rapidly progressive signs of toxicity [1][4][5][6][7].
ECG abnormalities [1][5] and hyperkalemia typically resolve within 4 hours after digoxin immune Fab administration [5].

Administration

Reconstitute the vial (40 mg) with 4 mL of Sterile Water for Injection and mix gently; the final concentration will be approximately 10 mg/mL (see Special Considerations section for storage and stability of the reconstituted vial). May dilute the reconstituted solution to an appropriate volume of NS for administration. Very small doses (less than 1 mL) may be given undiluted via a tuberculin syringe or the reconstituted solution may be further diluted with 36 mL of NS to achieve a 1 mg/mL concentration. Administer by slow IV infusion over 30 minutes; if cardiac arrest is imminent, the solution can be given by bolus injection [1].
Stop temporarily the IV infusion for any infusion-rate related anaphylactoid reactions (eg, hypotension, wheezing, urticaria) and restart at a lower rate. Incidence of infusion-related reactions may be increased with bolus injection [1].

MEDICATION SAFETY

Contraindications/Precautions

Anaphylaxis and hypersensitivity reactions may occur; higher risk in patients with sheep protein allergies or who have previously received intact ovine antibodies or ovine Fab.
Patients with poor cardiac function may deteriorate upon loss of inotropic effect of digoxin.
Hypokalemia may occur; monitoring recommended [1].

Adverse Effects

The most common adverse reactions are worsening congestive heart failure (13%), hypokalemia (13%) and worsening atrial fibrillation (7%) [1].

Monitoring

Monitor serum digoxin serum concentration before digoxin immune Fab administration, if possible, to establish the digitalis intoxication diagnosis. Serum digoxin concentrations may be inaccurate for a period of time (several days or a week, or more in patients with renal impairment) after administration due to interference with digitalis immunoassay

measurements. Monitor temperature, blood pressure, and ECG during and after administration. Monitor potassium levels frequently, particularly during the first several hours after administration. Consider assessing free digoxin levels after administration in patients with renal failure to detect a possible recurrence of toxicity. Monitor for signs and symptoms of hypersensitivity reactions [1].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Digoxin immune Fab (ovine) is a sterile, lyophilized preparation of digoxin-immune ovine Fab (monovalent) immunoglobulin fragments obtained from the blood of healthy sheep. Digoxin immune Fab referentially binds molecules of digoxin or digitoxin, and the complex is then excreted by the kidneys. As free serum digoxin is removed, tissue-bound digoxin is also released into the serum to maintain the equilibrium and is bound and removed by digoxin immune Fab. The net result is a reduction in serum and tissue digoxin. Distributes extensively in the extracellular fluid. Digoxin-specific Fab fragments are excreted in the urine. The elimination half-life in patients with normal renal function is approximately 15 hours. In patients with renal impairment, the half-life may be increased by up to 10-fold [1]. Poorly removed by hemodialysis [4].

ABOUT

Special Considerations/Preparation

Available as a vial containing 40 mg of digoxin immune Fab protein. Store in refrigerator; do not freeze. Reconstitute the vial with 4 mL of Sterile Water for Injection and mix gently; the final concentration will be approximately 10 mg/mL. May dilute the reconstituted solution with NS to a concentration of 1 mg/mL for small doses or to an appropriate volume of NS for administration. Use reconstituted product immediately; if not used immediately, refrigerate and use within 4 hours [1].

Digoxin

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Loading dose ("Digitalization"): Generally used only when treating arrhythmias and acute congestive heart failure. Give over 24 hours as 3 divided doses.
Oral doses should be 25% greater than IV doses. Do not administer IM.

Note: These beginning doses are based primarily on studies that measured echocardiographic changes and EKG signs of toxicity and take into account renal maturation. Titrate dosage based on clinical response. Decrease dose proportional to the reduction in creatinine clearance.

Total Loading Dose		
PMA weeks	**IV mcg/kg/total dose**	**Oral mcg/kg/total dose**
	Divide total dose into 3 doses over 24 hours	**Divide total dose into 3 doses over 24 hours**
≤29	15	20
30 to 36	20	25
37 to 48	30	40
≥49	40	50

Maintenance Doses			
PMA weeks	**IV mcg/kg/dose**	**Oral mcg/kg/dose**	**Interval hours**
≤29	4	5	24
30 to 36	5	6	24
37 to 48	4	5	12
≥49	5	6	12
Titrate based on clinical response.			

Uses

Heart Failure or Arrhythmias
Treatment of heart failure caused by diminished myocardial contractility. Treatment of SVT, atrial flutter, and atrial fibrillation.

In neonates with pulmonary hypertension, supportive care with digitalis may be used cautiously for signs of right-sided heart failure; however, the data are limited and digoxin is rarely used in the pediatric population. Digoxin is not effective for acute deterioration [3].

Administration

Intravenous: Infuse concentrations of 20 mcg/mL or 100 mcg/mL over 15 to 30 minutes [1].
Oral: Give consistently with regard to feedings [2].

MEDICATION SAFETY

Contraindications/Precautions

Contraindicated with ventricular fibrillation or a history of hypersensitivity to digoxin or other digitalis preparations [4].

Use caution in patients with low body weight, hypokalemia, hypomagnesemia, hypercalcemia, and renal impairment, as risk of digoxin toxicity is higher in these patients; monitoring and dose adjustment may be required. Wolff-Parkinson-White syndrome patients with atrial fibrillation have an increased risk of ventricular fibrillation. Severe sinus bradycardia or sinoatrial block may occur, especially in patients with preexisting sinus node disease or incomplete atrioventricular block; consider pacemaker placement before initiating treatment. Decreased cardiac output may develop with use in patients with heart failure associated with preserved left ventricular systolic function. May induce ventricular arrhythmias in patients undergoing electrical cardioversion; consider reducing dose or discontinuing use 1 to 2 days prior to procedure. Avoid use in patients with myocarditis; use not recommended in patients with acute myocardial infarction. Drugs that affect renal function (eg, ACE inhibitors, angiotensin receptor blockers, NSAIDs, COX-2 inhibitors) may increase digoxin exposure [4][2].

Adverse Effects

Toxic Cardiac Effects:
- PR interval prolongation
- Sinus bradycardia or SA block
- Atrial or nodal ectopic beats
- Ventricular arrhythmias

Nontoxic Cardiac Effects:

- QTc interval shortening
- ST segment sagging
- T-wave amplitude dampening
- Heart rate slowing

Other Effects: Feeding intolerance, vomiting, diarrhea, and lethargy.

Treatment of Life-Threatening Digoxin Toxicity:
Digibind® Digoxin Immune Fab, IV over 30 minutes through 0.22-micron filter.

Dose (# of vials) = (weight [kg]) x (serum digoxin concentration)/100

Each vial of digibind contains 38 mg (enough to bind 0.5 mg Digoxin).

Solution Compatibility

(only when diluted 4-fold or greater): D_5W, $D_{10}W$, NS, and sterile water for injection.

Terminal Injection Site Compatibility

Cimetidine, famotidine, furosemide, heparin, hydrocortisone succinate, insulin, lidocaine, linezolid, meropenem, midazolam, milrinone, morphine, potassium chloride, ranitidine, and remifentanil.

Terminal Injection Site Incompatibility

Amiodarone, dobutamine, fluconazole, and propofol.

Monitoring

Follow heart rate and rhythm closely. Periodic EKGs to assess both desired effects and signs of toxicity. Follow closely (especially in patients receiving diuretics or amphotericin B) for decreased serum potassium and magnesium, or increased calcium and magnesium, all of which predispose to digoxin toxicity. Assess renal function. Be aware of drug interactions. May follow serum drug concentrations if assay is available that excludes endogenous digoxin-like substances. Therapeutic serum concentration is 1 to 2 nanograms/mL.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Digitalis glycoside with positive inotropic and negative chronotropic actions. Increases myocardial catecholamine levels (low doses) and inhibits sarcolemmal sodium-potassium-ATPase (higher doses) to enhance contractility by increasing systolic intracellular calcium-ion concentrations. Indirectly increases vagal activity, thereby slowing S-A node firing and A-V node conduction. Other effects include peripheral, splanchnic, and perhaps, pulmonary vasoconstriction, and reduced CSF production. Serum concentration peaks 30 to 90 minutes after an oral dose, with myocardial peak occurring in 4 to 6 hours. Large volume of distribution that increases with age during infancy. Rapid absorption of oral dose from small intestine; reduced by antacids and rapid transit times. 20% protein bound. Probably not significantly metabolized. Glomerular filtration and tubular secretion account for most of the total body clearance of digoxin, although significant nonrenal elimination has been proposed.

ABOUT

Special Considerations/Preparation

Pediatric dosage forms: Injectable (100 mcg/mL) and elixir (50 mcg/mL).
Store at room temperature and protect from light.
Dilute injectable as follows:
1) Draw up digoxin into syringe.
2) Inject desired amount of drug into second syringe containing a 4-fold or greater volume of solution-compatible diluent. Use diluted product immediately.

Drug Interactions: Amiodarone, indomethacin, spironolactone, quinidine, and verapamil decrease digoxin clearance. Cisapride and metoclopramide decrease digoxin absorption. Spironolactone interferes with radioimmunoassay. Erythromycin may increase digoxin absorption.

DOSING/ADMINISTRATION

Dose

Usual dose: 2 to 25 mcg/kg per minute continuous IV infusion. Begin at a low dose and titrate by monitoring effects. Use a large vein for IV.

Uses

Hypoperfusion and Hypotension: Treatment of hypoperfusion and hypotension, especially if related to myocardial dysfunction.

Severe Sepsis and Septic Shock[4][5]

<table>
<tr><td colspan="3">Hemodynamic Support - First 60 Minutes</td></tr>
<tr><td>Time</td><td colspan="2">Management- Proceed to next step if shock persists</td></tr>
<tr><td>0 minutes</td><td colspan="2">Maintain airway and establish access</td></tr>
<tr><td>5 minutes</td><td colspan="2">Push 10 mL/kg isotonic crystalloid or colloid boluses up to 40 mL/kg until improved perfusion or unless hepatomegaly.
Begin prostaglandin infusion until rule out ductal-dependent lesion.</td></tr>
<tr><td rowspan="2">15 minutes</td><td colspan="2">DOPamine less than 10 mcg/kg/min +/- DOBUTamine for fluid-refractory shock</td></tr>
<tr><td colspan="2">EPINEPHrine 0.05 to 0.3 mcg/kg/min for fluid-refractory DOPamine-resistant shock</td></tr>
<tr><td>60 min</td><td>Cold shock-Poor LV function
Normal blood pressure
ScvO(2) less than 70%*/Hgb greater than 12 g/dL
SVC flow less than 40 mL/kg/min or CI less than 3.3 L/min/m(2)</td><td>Add nitrovasodilator milrinone or inamrinone with volume loading</td></tr>
</table>

	Cold shock- Poor RV function PPHN ScvO(2) less than 70%* SVC flow less than 40 mL/kg/min or CI less than 3.3 L/min/m(2)	Inhaled nitric oxide Inhaled iloprost or IV adenosine IV milrinone or inamrinone
	Warm shock- Low blood pressure	Titrate volume Add norepinephrine Vasopressin or terlipressin or angiotensin
	Refractory shock	Hydrocortisone if absolute adrenal insufficiency. Triiodothyronine if hypothyroid. Begin pentoxifylline if VLBW newborn. Consider closing PDA if hemodynamically significant.
	ECMO	
Goals •First Hour: restore and maintain heart rate thresholds, capillary refill of 2 seconds or less, and normal blood pressure. • NICU: normal MAP-CVP, preductal and postductal oxygen saturation difference less than 5%, *ScvO(2) greater than 70% (except congenital heart patients with mixing lesions), SVC flow greater than 40 mL/kg/min, or cardiac index greater than 3.3 L/min/m(2)		
KEY: CI = cardiac index, Hgb = hemoglobin, LV function = left ventricle function, MAP-CVP = mean arterial pressure-central venous pressure, PDA = patent ductus arteriosus, PPHN = persistent pulmonary hypertension of the newborn, ScvO(2) = continuous central venous oxygen saturation, SVC = superior vena cava, VLBW = very low birth weight		
Davis et al: Crit Care Med 2017;45(6)		

Administration

May administer by IV or IO route as a continuous infusion. Avoid bolus administration of the drug. Infusion into a large vein is preferred to minimize risk of tissue extravasation. Vials must be diluted prior to use in compatible diluent up to a concentration of 4000 mcg/mL. Solutions containing DOBUTamine may exhibit a pink color which will increase with time due to oxidation of the drug. There is no significant loss of potency over 24 hours [1][2]. The recommended concentration in neonates is 2000 mcg/mL [3].

Solution Preparation Calculations
To calculate the AMOUNT of drug needed per defined final fluid volume:
Desired final concentration (mg/mL) x defined final fluid volume (mL) = AMOUNT of drug to add to final infusion solution (mg).
To calculate the VOLUME of drug needed per defined final fluid volume:
*AMOUNT of drug to add (mg) ÷ drug (vial) concentration (mg/mL) = VOLUME of drug to add (mL)
Example (for DOBUTamine): 30 mL of 2000 mcg/mL solution using DOBUTamine concentration of 12.5 mg/mL.
2000 mcg/mL = 2 mg/mL
2 mg/mL x 30 mL = 60 mg DOBUTamine
***60 mg ÷ 12.5 mg/mL = 4.8 mL of DOBUTamine**
Add 4.8 mL of DOBUTamine (12.5 mg/mL) to 25.2 mL of compatible solution (eg, D_5 W) to yield 30 mL of infusion solution with a concentration of 2000 mcg/mL.

Dobutamine Titration Chart		
Concentration (mcg/mL)	**Dose (mcg/kg/min)**	**IV Rate (mL/kg/hour)**
2000	2.5	0.075
	5	0.15
	7.5	0.23
	10	0.3

MEDICATION SAFETY

Adverse Effects

Cardiovascular: Dysrhythmias; increased pulmonary capillary wedge pressure (pulmonary congestion and edema) [6]. Increased heart rate and blood pressure; precipitous decrease in blood pressure [7].

Dermatologic: Phlebitis; local inflammatory changes observed with inadvertent infiltration [7].

Solution Compatibility

D_5W, D_5NS, $D_{10}W$, LR, and NS.

Terminal Injection Site Compatibility

Alprostadil, amiodarone, atropine, aztreonam, caffeine citrate, calcium chloride, calcium gluconate, caspofungin, ceftazidime, ciprofloxacin, dopamine, enalaprilat, epinephrine, famotidine, fentanyl, fluconazole, flumazenil, heparin, hydralazine, insulin, isoproterenol, lidocaine, linezolid, lorazepam, magnesium sulfate, meropenem, midazolam, milrinone, morphine, nicardipine, nitroglycerin, nitroprusside, pancuronium bromide, phentolamine, potassium chloride, procainamide, propofol, propranolol, ranitidine, remifentanil, vecuronium, and zidovudine.

Terminal Injection Site Incompatibility

Acyclovir, alteplase, aminophylline, cefepime, bumetanide, diazepam, digoxin, furosemide, ibuprofen lysine, indomethacin, micafungin, phenytoin, phytonadione, piperacillin-tazobactam, and sodium bicarbonate.

Monitoring

Continuous heart rate and intra-arterial blood pressure monitoring preferable. Observe IV site for signs of extravasation.

For a full-term newborn, the target heart rate and perfusion pressure (mean arterial pressure minus central venous pressure) are 110 to 160 beats/min and 55 mm Hg, respectively [4].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Synthetic catecholamine with primarily β_1-adrenergic activity. Inotropic vasopressor. Increases myocardial contractility, cardiac index, oxygen delivery, and oxygen consumption. Decreases systemic and pulmonary vascular resistance (adults). DOBUTamine has a more prominent effect on cardiac output than dopamine but less of an effect on blood pressure. Onset of action is 1 to 2 minutes after IV administration, with peak effect in 10 minutes. Must be administered by continuous IV infusion because of rapid metabolism of drug. Serum half-life is several minutes. Metabolized in the liver by sulfoconjugation to an inactive compound. There is wide interpatient variability in plasma clearance due to differences in metabolism

and renal excretion.

ABOUT

Special Considerations/Preparation

Supplied as 250 mg per 20-mL vial (12.5 mg/mL) and premixed bags in concentrations of 1, 2, and 4 mg/mL. Diluted solutions for infusion should be used within 24 hours. Solutions containing DOBUTamine and dextrose may exhibit a pink color which will increase with time due to oxidation of the drug. There is no significant loss of potency.

There are no specific data regarding the compatibility of DOBUTamine and fat emulsions. DOBUTamine is most stable in solutions with a pH at or below 5. In alkaline solutions, the catechol moieties are oxidized, cyclized, and polymerized to colored materials. All fat emulsions have pH ranges from 6 to 9. Caution is urged when co-infusing DOBUTamine and fat emulsion together; DOBUTamine may degrade over time in this alkaline pH resulting in lower than expected clinical effects.

DOSING/ADMINISTRATION

Dose

Usual dose: 2 to 20 mcg/kg per minute continuous IV infusion. Begin at a low dose and titrate by monitoring effects; for fluid refractory shock start at less than 10 mcg/kg/min [1]. Use a large vein for IV.

Uses

Hypotension.

Severe Sepsis and Septic Shock[1][5]

<table>
<tr><td colspan="3">Hemodynamic Support - First 60 Minutes</td></tr>
<tr><td>Time</td><td colspan="2">Management- Proceed to next step if shock persists</td></tr>
<tr><td>0 minutes</td><td colspan="2">Maintain airway and establish access</td></tr>
<tr><td>5 minutes</td><td colspan="2">Push 10 mL/kg isotonic crystalloid or colloid boluses up to 40 mL/kg until improved perfusion or unless hepatomegaly.
Begin prostaglandin infusion until rule out ductal-dependent lesion.</td></tr>
<tr><td rowspan="2">15 minutes</td><td colspan="2">DOPamine less than 10 mcg/kg/min +/- DOBUTamine for fluid-refractory shock</td></tr>
<tr><td colspan="2">EPINEPHrine 0.05 to 0.3 mcg/kg/min for fluid-refractory DOPamine-resistant shock</td></tr>
<tr><td>60 min</td><td>Cold shock-Poor LV function
Normal blood pressure
ScvO(2) less than 70%*/Hgb greater than 12 g/dL
SVC flow less than 40 mL/kg/min or CI less than 3.3 L/min/m(2)</td><td>Add nitrovasodilator milrinone or inamrinone with volume loading</td></tr>
</table>

	Cold shock- Poor RV function PPHN ScvO(2) less than 70%* SVC flow less than 40 mL/kg/min or CI less than 3.3 L/min/m(2)	Inhaled nitric oxide Inhaled iloprost or IV adenosine IV milrinone or inamrinone
	Warm shock- Low blood pressure	Titrate volume Add norepinephrine Vasopressin or terlipressin or angiotensin
	Refractory shock	Hydrocortisone if absolute adrenal insufficiency. Triiodothyronine if hypothyroid. Begin pentoxifylline if VLBW newborn. Consider closing PDA if hemodynamically significant.
	ECMO	
Goals •First Hour: restore and maintain heart rate thresholds, capillary refill of 2 seconds or less, and normal blood pressure. • NICU: normal MAP-CVP, preductal and postductal oxygen saturation difference less than 5%, *ScvO(2) greater than 70% (except congenital heart patients with mixing lesions), SVC flow greater than 40 mL/kg/min, or cardiac index greater than 3.3 L/min/m(2)		
KEY: CI = cardiac index, Hgb = hemoglobin, LV function = left ventricle function, MAP-CVP = mean arterial pressure-central venous pressure, PDA = patent ductus arteriosus, PPHN = persistent pulmonary hypertension of the newborn, ScvO(2) = continuous central venous oxygen saturation, SVC = superior vena cava, VLBW = very low birth weight		
Davis et al: Crit Care Med 2017;45(6)		

There was no difference between epinephrine and dopamine for fluid-refractory septic shock in a randomized, double-blind controlled trial (n=40) in India; however, the study was underpowered. After persistent shock despite 2 boluses of normal saline 10 mL/kg, epinephrine 0.2 mcg/kg/min or dopamine 10 mcg/kg/min were started. Doses were increased, if needed, after 15 minutes to epinephrine 0.3 mcg/kg/min or dopamine 15

mcg/kg/min; then again, if needed, after another 15 minutes to epinephrine 0.4 mcg/kg/min or dopamine 20 mcg/kg/min. The mean gestational age was 30.3 weeks (1.1 kg birth weight) for epinephrine group and 30.7 weeks (1.181 kg birth weight) for dopamine group [6].

Administration

May administer by IV or IO route as a continuous infusion. Avoid bolus administration of the drug. Infusion into a large vein is preferred to minimize risk of tissue extravasation. Vials must be diluted prior to use in compatible diluent up to a concentration of 3200 mcg/mL [2][3]. The recommended standard neonate concentration is 1600 mcg/mL [4].

Solution Preparation Calculations
To calculate the AMOUNT of drug needed per defined final fluid volume:
Desired final concentration (mg/mL) × defined final fluid volume (mL) = AMOUNT of drug to add to final infusion solution (mg).
To calculate the VOLUME of drug needed per defined final fluid volume:
*AMOUNT of drug to add (mg) ÷ drug (vial) concentration (mg/mL) = VOLUME of drug to add (mL)
Example (for DOPamine): 30 mL of 1600 mcg/mL solution using DOPamine concentration of 40 mg/mL.
1600 mcg/mL = 1.6 mg/mL
1.6 mg/mL × 30 mL = 48 mg DOPamine
***48 mg ÷ 40 mg/mL = 1.2 mL of DOPamine**
Add 1.2 mL of DOPamine (40 mg/mL) to 28.8 mL of compatible solution (eg, D_5W) to yield 30 mL of infusion solution with a concentration of 1600 mcg/mL.

Dopamine Titration Chart

Concentration (mcg/mL)	Dose (mcg/kg/min)	IV Rate (mL/kg/hour)
1600	2.5	0.094
	5	0.19
	7.5	0.28
	10	0.38

MEDICATION SAFETY

Adverse Effects

Tachycardia and arrhythmias. May increase pulmonary artery pressure. Reversible suppression of prolactin and thyrotropin secretion.

Black Box Warning

Tissue sloughing may occur with IV infiltration. According to the manufacturer's black box warning, to prevent sloughing and necrosis in areas of extravasation, the area should be infiltrated as soon as possible with a saline solution containing phentolamine mesylate. **Suggested treatment for extravasation:** Inject a 0.5 mg/mL solution of phentolamine into the affected area. The usual amount needed is 1 to 5 mL, depending on the size of the infiltrate.

Solution Compatibility

D_5W, D_5NS, $D_{10}W$, LR, and NS.

Terminal Injection Site Compatibility

Aminophylline, amiodarone, aztreonam, caffeine citrate, calcium chloride, caspofungin, cefotaxime, cefoxitin, ceftazidime, chloramphenicol, dobutamine, enalaprilat, epinephrine, esmolol, famotidine, fentanyl, fluconazole, flumazenil, gentamicin, heparin, hydrocortisone succinate, ibuprofen lysine, lidocaine, linezolid, lorazepam, meropenem, metronidazole, micafungin, midazolam, milrinone, morphine, nicardipine, nitroglycerin, nitroprusside, oxacillin, pancuronium bromide, piperacillin/tazobactam, potassium chloride, propofol, prostaglandin E_1, ranitidine, tobramycin, vecuronium, and zidovudine.

Terminal Injection Site Incompatibility

Acyclovir, alteplase, amphotericin B, ampicillin, cefepime, furosemide, indomethacin, insulin, penicillin G, and sodium bicarbonate.

Monitoring

Continuous heart rate and intra-arterial blood pressure monitoring is preferable. Assess urine output and peripheral perfusion frequently. Observe IV site closely for blanching and infiltration.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Catecholamine that is metabolized rapidly. Serum half-life is 2 to 5 minutes, but clearance is quite variable. DOPamine increases blood pressure primarily by increasing systemic vascular resistance via α-adrenergic effects. Effects on cardiac output vary with gestational age and baseline stroke volume. Selective renal vasodilation associated with increases in urine output has been noted in preterm neonates at doses of 2 to 5 mcg/kg/minute. No changes in mesenteric or cerebral blood flow were observed. Mechanism of action in neonates is controversial. Relative effects of DOPamine at different doses are uncertain because of developmental differences in 1) endogenous norepinephrine stores, 2) α-adrenergic, β-adrenergic, and dopamine receptor functions, and 3) the ability of the neonatal heart to increase stroke volume. Responses tend to be individualized. Use higher doses with caution in patients with persistent pulmonary hypertension of the newborn.

ABOUT

Special Considerations/Preparation

Available in 40-mg/mL, 80-mg/mL, and 160-mg/mL vials for injection and premixed bags in concentrations of 800, 1600, and 3200 mcg/mL. Diluted solutions stable for 24 hours. **Admixtures exhibiting a color change should not be used.**

There are no specific data regarding the compatibility of DOPamine and fat emulsions. DOPamine is most stable in solutions with a pH at or below 5. In alkaline solutions, the catechol moieties are oxidized, cyclized, and polymerized to colored materials. All fat emulsions have pH ranges from 6 to 9. Caution is urged when co-infusing DOPamine and fat emulsion together; DOPamine may degrade over time in this alkaline pH resulting in lower than expected clinical effects.

Dornase alfa

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

1.25 mL to 2.5 mL via nebulizer, or 0.2 mL/kg instilled directly into the endotracheal tube. Administer once or twice per day.

Uses

Treatment of atelectasis secondary to mucus plugging, that is unresponsive to conventional therapies.

MEDICATION SAFETY

Adverse Effects

Desaturation and/or airway obstruction may occur due to rapid mobilization of secretions.

Monitoring

Monitor airway patency. Suction the airway as needed.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Pulmozyme® is a highly purified solution of recombinant human deoxyribonuclease (rhDNase, an enzyme that selectively cleaves DNA). The protein is produced by genetically engineered Chinese hamster ovary cells. Purulent pulmonary secretions contain very high concentrations of extracellular DNA released by degenerating leukocytes. rhDNase hydrolyzes this DNA to decrease the viscoelasticity of the secretions. Clinical improvements in the thickness of secretions and ventilation usually occur within 3 hours of administration.

ABOUT

Special Considerations/Preparation

Pulmozyme® is supplied in single-use ampules. Each ampule contains 2.5 mL of a sterile, clear, colorless, aqueous solution containing 1 mg/mL dornase alfa (2.5 mg per ampule), 0.15 mg/mL calcium chloride dihydrate, and 8.77 mg/mL sodium chloride (22 mg per ampule) with no preservative. The nominal pH of the solution is 6.3. The ampules should be stored in their protective foil pouch under refrigeration at 2 to 8 degrees C (36 to 46 degrees F) and protected from strong light. Do not use beyond the expiration date on the ampule [1].

DOSING/ADMINISTRATION

Dose

Anthrax
32 to 44 weeks postmenstrual age
Oral
• **32 to 37 weeks gestational age:** 5 mg/kg orally every 12 hours [1]
• **Full term neonates:** 5 mg/kg oral loading dose, then 2.5 mg/kg orally every 12 hours [1]
IV
• **32 to 37 weeks gestational age:** 5 mg IV every 12 hours; switch to oral therapy based on clinical improvement [1]
• **Full term neonates:** 5 mg/kg IV loading dose, then 2.5 mg/kg IV every 12 hours; switch to oral therapy based on clinical improvement [1]
Duration of therapy, postexposure prophylaxis: 60 days for aerosol exposure; 7 days for nonaerosol exposure (ie, cutaneous or ingestion) [1]
Duration of therapy, cutaneous anthrax: 7 to 10 days or until clinically stable. If aerosol exposure occurred or is suspected, transition to a postexposure prophylaxis regimen after completion of the treatment regimen for a total duration of 60 days [1].
Duration of therapy, systemic anthrax: At least 2 weeks; initiate with IV therapy and switch to oral based on clinical improvement. If aerosol exposure occurred or is suspected, transition to a postexposure prophylaxis regimen after completion of the treatment regimen for a total duration of 60 days [1].

Dosage Adjustments
Renal impairment: No adjustment necessary [2][3][4][5]
Hepatic impairment: No adjustment necessary [2]
Hemodialysis: No adjustment necessary [6]
Prolonged intermittent renal replacement therapy (PIRRT): No adjustment necessary [6]
Continuous renal replacement therapy: No adjustment necessary [6]

Uses

Anthrax Empiric Treatment Regimens for Preterm and Full-Term Infants 32 to 44 Weeks Postmenstrual Age

Recommended Regimen(s)*	Preferred Therapy if Penicillin Sensitive	Preferred if Penicillin Resistant or Awaiting Susceptibility Testing	Alternative Therapy
Postexposure prophylaxis			

• A single, oral (unless otherwise noted) antimicrobial drug	Amoxicillin	Ciprofloxacin	Moxifloxacin
	Penicillin VK	Clindamycin	Linezolid
	Penicillin G aqueous IM	Doxycycline	
	Amoxicillin/clavulanate	Levofloxacin	
Cutaneous anthrax			
• A single, oral (unless otherwise noted) antimicrobial drug	Amoxicillin	Ciprofloxacin	Moxifloxacin
	Penicillin VK	Doxycycline	Linezolid IV
	Amoxicillin/clavulanate	Clindamycin	Meropenem IV
		Levofloxacin	Vancomycin IV
			Omadacycline IV (34 weeks gestational age or older only)
			Dalbavancin IV (full term infants only)
Systemic anthrax with or without meningitis (administer with antitoxin)**			
• Two bactericidal drugs from different antimicrobial classes plus a PSI or RNAI (preferred unless contraindicated or not tolerated)	Bactericidal Drugs:	Bactericidal Drugs:	Bactericidal Drugs:
• One bactericidal drug plus a PSI	• Penicillin G aqueous IV/IM	• Ciprofloxacin	• Moxifloxacin
• Two bactericidal drugs from different antimicrobial classes	• Ampicillin	• Levofloxacin	• Imipenem/cilastatin (preferred agent if meningitis is confirmed)
• One bactericidal drug plus an RNAI		• Meropenem	• Dalbavancin (full term infants only)

• A PSI plus an RNAI		• Vancomycin	• Ampicillin/sulbactam (if penicillin sensitive)
• Two PSIs from different antimicrobial classes			
• A single bactericidal drug		PSI/RNAI:	PSI/RNAI:
• A single PSI		• Doxycyline	• Clindamycin
			• Linezolid
			• Rifampin
			• Omadacycline (34 weeks gestational age or older only)
Key: PSI = protein synthesis inhibitor; RNAI = RNA synthesis inhibitor			
* Recommended regimens and drugs listed in descending order of preference.			
** Initiate treatment with IV administration. Transition to oral administration based on patient improvement.			
[1]			

FDA Approved Pediatric Uses: Use of doxycycline is not recommended in infants and children younger than 8 years, except when the potential benefits are expected to outweigh the risks in severe or life-threatening conditions (e.g., anthrax, Rocky Mountain spotted fever) [13][7].

Administration

Oral:
Administer tablets and capsules with adequate amounts of fluid to wash down the drug and minimize esophageal irritation/ulceration [7].
Administer oral formulations with food or milk if gastric irritation occurs [8][9][10].

IV:
Avoid rapid administration [11].

Extravasation Management: Although not pediatric-specific, the following are recommendations for extravasation of acidic agents (doxycycline pH ranges from 1.8 to 3.3) [12]:

- **General:**
- Stop and disconnect infusion; do not remove the cannula or needle
- Attempt to gently aspirate as much extravasated agent as possible; avoid manual pressure
- Remove cannula or needle
- Dry heat and elevation
- Closely monitor for signs of coagulation and ischemia

- Avoid attempt at pH neutralization (doxycycline - pH 1.8 to 3.3)
- Monitor and consider the need for surgical management such as surgical flushing with normal saline or debridement and excision of necrotic tissue (especially if pain persists for 1 to 2 weeks). In cases of compartment syndrome, surgical decompression may be required
- **Refractory Events:**
- Hyaluronidase 15 units intradermally along injection site and edematous area. Give as five, 0.2 mL intradermal injections along extravasation site and edematous tissue.
- **Inadvertent Intraarterial Administration:**
- Leave inadvertent intraarterial line in place for diagnostics
- Systemic heparin titrated to therapeutic anticoagulant effect.
- Stellate ganglion block

MEDICATION SAFETY

Contraindications/Precautions

Contraindicated in patients hypersensitive to any of the tetracyclines [15][9][10][14].

PRECAUTIONS
Concomitant use: Isotretinoin; avoid use; increased risk of pseudotumor cerebri [16][17][18]
Dermatologic: Severe skin reactions, including exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported; discontinuation required [19][20][21][22]
Dermatologic: Photosensitivity may occur; discontinue at first sign of erythema [16][23][17][18]
Gastrointestinal: Clostridium difficile-associated diarrhea (mild diarrhea to fatal colitis) has been reported; may occur 2 months or more after treatment; if suspected or confirmed discontinue use [16][17][18]
Gastrointestinal: Use during tooth development (ie, last half of pregnancy, infancy and childhood up to 8 years of age) may cause permanent discoloration of the teeth and/or enamel hypoplasia with increased risk with long-term or repeat short-term use; avoid use in patients 8 years or younger except for cases of severe or life-threatening conditions (eg, anthrax, Rocky Mountain spotted fever), especially when alternative therapies are not available [21][22].
Immunologic: During malaria prophylaxis complete suppression of protozoal growth stages does not occur, thus, transmission of malaria, to mosquitoes outside endemic areas, after completion of regimen may occur [16][23]
Immunologic: Overgrowth of nonsusceptible organisms including fungi may occur; discontinue therapy if superinfection develops [16][17][18][23]
Musculoskeletal: Decreased skeletal growth in premature infants has been reported during therapy; generally reversible upon discontinuation [16][17][18][23]
Neurologic: Bulging fontanels may occur [23]
Neurologic: Intracranial hypertension (IH; pseudotumor cerebri), which may result in permanent vision loss, has been reported [23][17][18].

Renal: Dose-related increases in BUN may occur [21][22].

Adverse Effects

.
Bulging fontanels have been reported in infants [24][17][25][18]. Gastrointestinal effects such as anorexia, nausea, vomiting, and diarrhea may occur [9][26][14]. Rash, urticaria, and hemolytic anemia have also been reported [27].

Monitoring

Evaluate organ systems (eg, hematopoietic, renal, and hepatic studies) periodically during long-term therapy. Perform dark field examinations before initiating treatment and repeat blood serology monthly for at least 4 months for venereal disease with suspected coexistent syphilis [8][9][10][14].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action: Doxycycline inhibits bacterial protein synthesis by binding to the 30S ribosomal subunit, and has bacteriostatic activity against a broad range of Gram-positive and Gram-negative organisms [28]..

Clearance, younger than 2 years: 0.059 L/kg/hr [29]
Vd, younger than 2 years: 1.5 L/kg [29]
Half-life, younger than 2 years: 17.7 hours [29]

ABOUT

Special Considerations/Preparation

Availability (oral): Powder for oral suspension (25 mg/5 mL); oral syrup (50 mg/5mL); various tablet and capsule strengths ranging from 40 mg to 200 mg [30].
Storage: Store below 30 degrees C (86 degrees F) and protect from light [31][27][32][33] [8]

Availability (IV): 100- and 200-mg vials of lyophilized doxycycline [34].
Storage: Store vials at 20 to 25°C (68 to 77°F) and protect from light [34]

Preparation (IV)
• Reconstitute vial with 10 mL (100-mg vial) or 20 mL (200 mg vial) SWFI for a concentration

of 10 mg/mL [34]
• Further dilute with 100 to 1000 mL (100-mg vial) or 200 to 2000 mL (200-mg vial) of a compatible solution (ie, NS, D5W, LR) for a final concentration of 0.1 mg/mL to 1 mg/mL [34]
• Stable for 48 hours at 25°C under fluorescent light when diluted with NS or D5W; protect from direct sunlight during storage and infusion. May store for 72 hours if refrigerated and protected from sunlight and artificial light; in this situation, infusion time should not exceed 12 hours [34]
• When diluted with solutions other than NS or D5W (eg, LR), storage and stability information may differ. Please consult the manufacturer's product information [34]

Emergency Extemporaneous Preparation
Intended for use during a public health emergency for those who cannot swallow pills [35].
• Place one 100-mg **doxycycline hyclate** tablet in a small bowl [35].
• Add 20 mL water to bowl and allow to soak for at least 10 minutes to soften tablet [35].
• Crush tablet with back of a metal spoon until there are no visible pieces of tablet left; stir to mix [35].
• Measure the appropriate dosage and place into a second small bowl [35].
• Mix with 3 teaspoons of milk, formula, breastmilk, chocolate milk, chocolate pudding, or a solution of apple juice plus 2 to 4 teaspoons of sugar; stir well [35].
• For children 23 kg or less, may store leftover doxycycline and water mixture in a covered bowl or cup at 20 to 25°C (68 to 77°F) for 24 hours [35].

DOSING/ADMINISTRATION

Dose

Daily Requirement: Recommendations from the American Society for Parenteral and Enteral Nutrition [1].

Daily Electrolyte and Mineral Requirements*		
Electrolyte	Preterm neonates	Infants/children
Sodium	2 to 5 mEq/kg/day	2 to 5 mEq/kg/day
Potassium	2 to 4 mEq/kg/day	2 to 4 mEq/kg/day
Calcium	2 to 4 mEq/kg/day	0.5 to 4 mEq/kg/day
Phosphorus	1 to 2 mmol/kg/day	0.5 to 2 mmol/kg/day
Magnesium	0.3 to 0.5 mEq/kg/day	0.3 to 0.5 mEq/kg/day
Acetate	As needed to maintain acid-base balance	As needed to maintain acid-base balance
Chloride	As needed to maintain acid-base balance	As needed to maintain acid-base balance
*Assumes normal age-related organ function and normal losses.		

Emtricitabine

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Prior to or during initiation, test patients for hepatitis B virus infection[1].

HIV Infection
3 mg/kg orally once daily [1].

Hepatitis B with HIV co-infection
Dosage: 6 mg/kg orally daily, **MAX 200 mg**[2]
2 to less than 12 years: 6 mg/kg orally daily (**MAX 200 mg**), plus tenofovir disoproxil fumarate 8 mg/kg orally once daily (**MAX 300 mg**) [2]
12 years and older: 200 mg orally once daily, plus tenofovir disoproxil fumarate 300 mg orally once daily OR tenofovir alafenamide 10 or 25 mg orally daily [3]

Dose Adjustments
Renal Impairment
There are no published recommendations available for dose adjustment in neonatal patients with renal impairment. Since elimination of emtricitabine is primarily dependent on CrCl, dose adjustments in neonates should be similar to CrCl-based dose adjustments for adults. The following dose adjustments are consistent with recommendations in adult patients with renal impairment [4]:
CrCl 30 to 49 mL/min: 1.5 mg/kg (0.15 mL/kg) every 24 hours.
CrCl 15 to 29 mL/min: 1 mg/kg (0.1 mL/kg) every 24 hours.
CrCl less than 15 mL/min or receiving hemodialysis: 0.75 mg/kg (0.075 mL/kg) every 24 hours; give dose after hemodialysis on hemodialysis days.

Uses

Antiretroviral Management in the Newborn: [5]

Risk of HIV in Newborn	Description	Antiretroviral (ARV) Management †
Low risk of transmission	Infants 37 weeks or older gestation when the mother: • is currently receiving or has received 10 consecutive weeks	Zidovudine for 2 weeks (footnote 1)

	of ART during pregnancy, and • has achieved and maintained or maintained viral suppression (2 consecutive tests with HIV RNA levels less than 50 copies/mL obtained at least 4 weeks apart) for the duration of pregnancy, and • has HIV RNA <50 copies/mL at or after 36 weeks and within 4 weeks of delivery, and • did not have acute HIV infection during pregnancy, and • has reported good ART adherence, and adherence concerns have not been identified	
	•Infants born to mothers who do not meet the criteria above but who have HIV RNA <50 copies/mL at or after 36 weeks gestation	Zidovudine for 4 to 6 weeks (footnote 1)
	Premature infants (<37 weeks gestation) who are not at high risk of perinatal acquisition of HIV	
Higher risk of transmission	•Mother has not received antepartum or intrapartum ARV therapy, or •Mother has received only intrapartum ARV	Zidovudine, lamivudine, and nevirapine for 2 to 6 weeks; if duration of the 3-drug regimen is shorter than 6 weeks,

	therapy, or •Mother has received antepartum and intrapartum ARV drugs but does not have viral suppression within 4 weeks prior to delivery, or •Mother has acute or primary HIV infection during pregnancy or breastfeeding (footnote 2)	zidovudine should be continued to complete 6 weeks of prophylaxis (footnote 3)
		Zidovudine, lamivudine, and raltegravir for 2 to 6 weeks; if duration of the 3-drug regimen is shorter than 6 weeks, zidovudine should be continued to complete 6 weeks of prophylaxis (footnote 3)
Presumed exposure	•Mother with unknown HIV status who test positive at delivery or postpartum, or whose newborn has positive HIV antibody test	•ARV management is the same as those with higher risk of transmission (see above). •Discontinue immediately if supplemental testing confirms mother does not have HIV.
Confirmed (footnote 4)	•Confirmed positive newborn HIV virologic test/nucleic acid test	Three-drug ARV regimen using treatment doses. The preferred regimen in newborns is 2 NRTIs plus nevirapine or raltegravir
Footnotes: 1. Zidovudine prophylaxis is recommended for infants born to mothers with HIV-2 mono-infection. If mother has HIV-1 and HIV-2 co-infection, the ARV regimen should be determined based on risk. Raltegravir should be considered in patients at high risk of perinatal HIV-2 acquisition		

because HIV-2 is not susceptible to nevirapine 2. Most panel members opt to administer presumptive HIV therapy to infants born to mother with acute HIV infection due to the higher risk of in utero transmission. If acute HIV is diagnosed during breastfeeding, the mother should immediately discontinue breast feeding 3. The optimal duration of presumptive HIV therapy in newborns with high risk for HIV acquisition is unknown. Patients should receive the zidovudine portion of the three-drug regimen for 6 weeks. The other two ARVs (emtricitabine/nevirapine or emtricitabine/raltegravir may be administered for 2 to 6 weeks. The recommended duration of treatment with the three-drug regimen varies depends on HIV NAT results, maternal viral load at time of delivery, and additional risk factors for HIV transmission including breastfeeding 4. ART should be initiated without waiting for results of confirmatory HIV NAT testing. However, the specimen for confirmatory testing should be attained prior to ART initiation
Reference: https://clinicalinfo.hiv.gov /en/guidelines/pediatric-arv/whats-new April 2022

Pediatric FDA Approved Indications
Treatment of HIV-1 infection, in combination with other antiretroviral agents, in children starting at birth [4].

Administration

May be administered with or without feedings [4].

MEDICATION SAFETY

Contraindications/Precautions

Precautions
Hepatic: Lactic acidosis and severe hepatomegaly with steatosis, including fatalities, have been reported; suspend treatment if lactic acidosis or hepatotoxicity (including hepatomegaly and steatosis) are suspected, even without marked elevations in transaminases [1]
Immunologic: Autoimmune disorders, including Graves disease, polymyositis, and Guillain-Barré syndrome, have been reported in the setting of immune reconstitution; may occur

many months after initiation of therapy [1]
Immunologic: Immune reconstitution syndrome has been reported; inflammatory response to opportunistic infections (eg, Mycobacterium avium, cytomegalovirus, Pneumocystis jirovecii pneumonia, TB) may occur during initial phase of antiretroviral therapy [1]
Renal: Dose adjustment recommended in patients with CrCl of less than 50 mL/min or receiving hemodialysis treatment; monitoring recommended [1]

Adverse Effects

In a 96-week, phase 2, open-label, non-randomized, multicenter study of HIV-infected pediatric patients 3 months to 17 years of age (n=116), skin discoloration, presenting as small, asymptomatic maculae on the palms or soles, occurred in 13% (annual incidence rate) of patients. All cases were mild (grade 1) and self-limiting with one exception (moderate, grade 2). Other common adverse events (all reported as annual incidence rates) were the following: infection (26%), increased cough (17%), otitis media (13%), rhinitis (13%), vomiting (12%), rash (11%), diarrhea (10%), pneumonia (8%), and gastroenteritis (8%). Grade 3 or 4 adverse events considered to be probably or possibly related to emtricitabine included leukopenia, anemia, gastroenteritis, and pancreatitis, all occurring at a frequency of less than 1% (annual incidence rate) [7].

Gastrointestinal

Pancreatitis has been reported with the use of NRTIs and ritonavir-boosted PIs; discontinue the offending agent and avoid reintroduction [6].

Lactic acidosis

Lactic acidosis has been reported with emtricitabine use. Consider discontinuing ARV drugs temporarily in patients with a lactate 2.1 to 5 mmol/L (confirmed with second test) while conducting additional diagnostic work-up. In patients with a lactate 5 mmol/L or greater (confirmed with second test) or 10 mmol/L (any one test), discontinue all ARV drugs and provide supportive therapy (eg, IV fluids, sedation, respiratory support). Following resolution of clinical and laboratory abnormalities, resume therapy with either an NRTI-sparing regimen or a revised NRTI-containing regimen. Monitor lactate monthly for 3 months or more [6].

Black Box Warning

Severe acute exacerbations of hepatitis B (HBV) have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued emtricitabine. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are coinfected with HIV-1 and HBV and discontinue emtricitabine. If appropriate, initiation of anti-hepatitis B therapy may be warranted [1].

Monitoring

[6]

Antiretroviral Monitoring in Children (adjust schedule based on the specific antiretroviral regimen)							
	Entry into Care†	ART Initiation ††	1 to 2 weeks after initiation	2 to 4 weeks after initiation	Every 3 to 4 months †††	Every 6 to 12 months ‡	Virologic Failure (Prior to switching ARV regimen)
	If clinical, immunologic, or virologic deterioration is suspected, perform more frequent CD4 cell count and plasma viral load monitoring. If toxicity noted, perform testing more frequently until toxicity resolved						
Medical History and Physical Examination ‡‡, ‡‡‡	X	X	X	X	X		X
Adherence Evaluation ‡‡‡		X	X	X	X		X
CBC with differential †††	X	X		X	X		X
Chemistries †††, ♦♦	X	X		X	X		X
Lipid Panel ‡	X	X				X	
Random Plasma Glucose ♦♦♦		X				X	
Urinalysis	X	X				X	
CD4 count	X	X			X		X
Plasma Viral Load ♦	X	X		X	X		X
Resistance Testing	X						X
Hepatitis B screening ¶	X						X
Pregnancy Test for Girls and Young Women of Childbearing Potential	X	X					X

HLA-B*5701 ¶¶	X						

KEY: ARV = Antiretroviral; ART = Antiretroviral therapy; CBC = complete blood count

† If a child does not initiate ART after receiving an HIV diagnosis, the child's CD4 count and plasma viral load should be monitored at least every 3 to 4 months.

†† If ART is initiated within 30 to 90 days of a pre-therapy laboratory result, repeat testing may not be necessary.

††† CD4 cell count, CBC, and chemistries can be monitored less frequently (every 6 to 12 months) in children and youth who are adherent to therapy and have CD4 cell count values well above the threshold for opportunistic infection risk, have sustained viral suppression, and have stable clinical status for more than 2 to 3 years. Viral load testing every 3 to 4 months is generally recommended to monitor ARV adherence.

‡ If lipids have been abnormal in the past, more frequent monitoring might be needed. For patients treated with TDF, more frequent urinalysis should be considered.

‡‡ Pay special attention to changes in weight that might occur after altering an ARV regimen. Weight gain or weight loss may occur when using some ARV drugs.

‡‡‡ Virtual visits may be appropriate at some times points, particularly for adherence assessments and for visits for established patients.

♦ Some experts monitor viral load more often (with each injection) in adolescents initiating injectable cabotegravir and rilpivirine (CAB and RPV). Viral load monitoring should be performed 4 to 8 weeks after switching to long-acting CAB and RPV. HIV-RNA also should be checked in patients with unplanned missed visits and delayed dosing of long-acting CAB and RPV. When viremia develops during long-acting therapy, resistance testing, including integrase resistance testing, should be performed. Follow-up dosing in patients with missed doses should not be delayed while waiting for viral load and resistance test results. However, regimen changes should be prompted if resistance to CAB and/or RPV is discovered.

♦♦ Refers to a comprehensive metabolic panel. Some experts perform a comprehensive panel at entry and routinely test Cr, ALT, AST, with additional tests tailored to the history of the individual patient

♦♦♦ Random plasma glucose is collected in gray-top blood collection tube or other designated tube. Some experts would consider monitoring HgbA1C, rather than blood glucose, in children at risk for prediabetes/diabetes.

¶ Only recommended for individuals who have previously demonstrated no immunity to HBV and who are initiating a regimen that contains ARV drugs with activity against HBV (ie, lamivudine, emtricitabine, tenofovir alafenamide, or tenofovir disoproxil fumarate).

¶¶ Conduct HLA-B*5701 on entry prior to initiating abacavir if not done previously. Choose an alternative ARV drug if the patient is HLA-B*5701 positive.

Reference: https://clinicalinfo.hiv.gov/en/guidelines/pediatric-arv/whats-new April 2023

CD4 Cell Count and Percentages in Healthy Children							
	0 to 3 months	3 to 6 months	6 to 12 months	1 to 2 years	2 to 6 years	6 to 12 years	12 to 18 years
CD4 cell count (footnote 1)	2600 (1600 to 4000)	2850 (1800 to 4000)	2670 (1400 to 4300)	2160 (1300 to 3400)	1380 (700 to 2200)	980 (650 to 1500)	840 (530 to 1300)
CD4 percentage (footnote 1)	52 (35 to 64)	46 (35 to 56)	46 (31 to 56)	41 (32 to 51)	38 (28 to 47)	37 (31 to 47)	41 (31 to 52)
1. Values presented as median (10th to 90th percentile)							
Reference: https://clinicalinfo.hiv.gov/en/guidelines/pediatric-arv/whats-new April 2023							

In patients co-infected with HBV and HIV who have discontinued emtricitabine, monitor liver function closely for at least several months after discontinuing therapy [1].
Monitor renal function in patients with moderate to severe renal impairment [1].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Emtricitabine a synthetic nucleoside analog with activity against HIV-1 reverse transcriptase and HBV DNA polymerase, and is consistently 4 to 10 times more potent than lamivudine, the other NRTI with similar activity. Mean absolute bioavailability of emtricitabine is 93% and 75% for the capsules and the oral solution, respectively, and the relative bioavailability of the oral solution is approximately 80% of the capsules [4][8]. In a pharmacokinetic study in infants younger than 3 months (n=20), after receipt of two short course of emtricitabine oral solution (each 3 mg/kg once daily for 4 days) during the first 3 months of life, emtricitabine exposure was similar to the exposures achieved in patients 3 months to 17 years of age with a 6 mg/kg-dose and adults with a 200-mg dose. Emtricitabine AUC decreased with increasing age over the first 3 months of life, correlating with an increase in total body clearance of the drug [9]. Rapidly and extensively absorbed following oral administration with peak plasma concentrations occurring at 1 to 2 hours post-dose. Protein binding is less than 4%. Primarily eliminated renally. Following emtricitabine administration, approximately 86% and 14% of the dose was recovered in the urine and feces, respectively. Clearance is decreased in patients with renal impairment. Half-life is approximately 12 hours in neonates [4].

ABOUT

Special Considerations/Preparation

Availability: Oral solution 10 mg/mL.
Storage: Refrigerate oral solution at 2 to 8 degrees C (36 to 46 degrees F). If stored at room temperature, the oral solution is stable for up to 90 days, and any unused portion must be discarded after this time [4].

Enalapril maleate

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Begin with 40 mcg/kg per dose (0.04 mg/kg per dose) given orally every 24 hours. Usual maximum dose 150 mcg/kg per dose (0.15 mg/kg per dose), as frequently as every 6 hours. Titrate subsequent doses and interval based on amount and duration of response. Dosage may need to be increased every few days.

Uses

Treatment of moderate to severe hypertension. Afterload reduction in patients with congestive heart failure.

MEDICATION SAFETY

Contraindications/Precautions

Use with extreme caution in patients with impaired renal function: oliguria and increased serum creatinine occur frequently.

Adverse Effects

The most common adverse event in *infants* (cohort study; n=662) younger than 120 days, including term and preterm infants without significant congenital anomalies, on enalapril were hyperkalemia (13%), elevated serum creatinine (5%), hypotension (4%), and death (0.5%). Risk factors for adverse events were postnatal age younger than 30 days at first exposure and longer duration of therapy [1].
The CrCl significantly decreased in preterm and term neonates with cardiovascular disease after initiation of ACEIs (captopril or enalapril) in a retrospective review (n=206). The body surface area was less than 0.33 m^2 for all neonates [2].

Monitoring

Frequent assessment of blood pressure, particularly after the first dose. Periodic assessment of renal function and serum potassium.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Enalapril is a prodrug that is hydrolyzed in the liver to form the active ACE inhibitor enalaprilat, which blocks the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor. It thereby decreases plasma and tissue concentrations of angiotensin II and aldosterone, and increases plasma and tissue renin activity. Enalaprilat also prevents the breakdown of bradykinin, a potent vasodilator. Vascular resistance is reduced without reflex tachycardia. Beneficial effects are thought to be caused by a combination of afterload reduction and long-term inhibition of salt and water retention. Bioavailability of oral dosage form is uncertain in neonates, but is significantly less than the 60% reported in adults. Onset of action after oral dose is 1 to 2 hours. Duration of action is quite variable in neonates, ranging from 8 to 24 hours.

ABOUT

Special Considerations/Preparation

Oral Powder for Solution: Available as a kit containing 1 bottle of enalapril maleate 150 mg powder for solution and 1 bottle of Ora-Sweet SF® diluent. Once reconstituted, solution contains 1 mg/mL of enalapril maleate. Store at room temperature; protect from moisture and from freezing [3].

Prepare oral solution by adding approximately 75 mL of supplied Ora-Sweet SF® diluent to 150-mL bottle of enalapril powder. Shake well for 30 seconds. Reopen the bottle and add the remaining diluent. Shake for an additional 30 seconds. Solution is stable for 60 days after reconstitution [3].

Oral Solution: Available in a ready-to-use oral solution containing 1 mg/mL of enalapril maleate in a 150-mL bottle [4].

Store under refrigerated conditions between 2 and 8 degrees C (36 and 46 degrees F). May be stored at a room temperature of 20 to 25 degrees C (68 to 77 degrees F) for up to 60 days. Protect from freezing or excessive heat [4].

Oral Tablets: Available as enalapril maleate 2.5-mg, 5-mg, 10-mg, and 20-mg oral tablets; also contains lactose. The 10-mg and 20-mg tablets also contain iron oxides. Protect from moisture [5].

Extemporaneous Preparation

To prepare 200 mL of a **1 mg/mL** suspension: Place ten 20-mg enalapril tablets in a

standard polyethylene terephthalate bottle. Add 50 mL of Bicitra® (sodium citrate 500 mg/5 mL and citric acid 334 mg/5 mL). Shake for at least 2 minutes; let concentrate stand for 60 minutes; then shake for at least 1 additional minute. Add 150 mL of Ora-Sweet SF® to the concentrate, shake well. Shake well before each use. Product stability is 30 days when refrigerated at 2 to 8 degrees C (36 to 46 degrees F) [5].

Oral suspension of enalapril maleate **1 mg/mL** was stable for 50 days at 5 degrees C or 30 days at room temperature. A buffer solution was prepared with citric acid 592 mg, hydrochloric acid 0.1 molar (M) 40.9 mL, sodium hydroxide 1 M 5.7 mL, and purified water 28.4 mL. Pure enalapril maleate powder 100 mg was dissolved in the solution and a simple syrup was added in sufficient quantity to achieve a final volume of 100 mL. The pH of the formulation was 2.55 to 2.78 [6].

Oral suspensions of enalapril maleate **0.1 mg/mL and 1 mg/mL**, prepared with either hydroxyethylcellulose 0.5% solution (sugar-free) or a 1:10 mixture of raspberry syrup and hydroxyethylcellulose 0.5% solution (sugar added), were stable with a minimum of 98% retention of initial concentration for at least 30 days at 4 and 25 degrees C. In both formulations, methyl hydroxybenzoate 0.2% was included as a preservative, and citric acid 1 M was used to adjust the pH to 3. Over the 30 days of storage, pH and viscosity were not significantly altered with either of the enalapril suspension formulations [7].

Oral solutions of enalapril **1 mg/mL**, using a citric acid buffer (pH 5) or a 1:1 mixture of Ora-Sweet® and Ora-Plus® as vehicles, were found to be stable for 91 days at both 4 and 25 degrees C with greater than 92% retention of labeled strength [8]. In another 60-day observation study, the stability of oral solutions of enalapril prepared with crushed tablets and 3 different vehicles (1:1 mixture Ora-Plus® and Ora-Sweet®; 1:1 mixture Ora-Plus® and Ora-Sweet SF®; cherry syrup) was confirmed with greater than 94% retention of the original strength during dark storage at 5 and 25 degrees C. No visual or olfactory changes were evident [9].

When admixed with deionized water, enalapril **1 mg/mL** was stable for 56 days at 25 degrees C with greater than 90% retention of labeled strength [8], which extended an earlier report of 30-day stability at 5 degrees C for both 0.1 and 1 mg/mL concentrations [10]. Tablet dosage forms were crushed, extracted in isotonic citrate buffer (pH 5), and filtered. Hydroxybenzoate preservative did not prevent enalapril degradation [10].

Enalaprilat

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Begin with 10 mcg/kg per dose (0.01 mg/kg per dose) IV over 5 minutes every 24 hours. Titrate subsequent doses and interval based on amount and duration of response. Dosage may need to be increased every few days.

Uses

Treatment of moderate to severe hypertension. Afterload reduction in patients with congestive heart failure.

Administration

Administer over 5 minutes undiluted, or diluted to a concentration as low as 0.025 mg/mL [1].

MEDICATION SAFETY

Contraindications/Precautions

Use with extreme caution in patients with impaired renal function: oliguria and increased serum creatinine occur frequently.

Adverse Effects

Hypotension occurs primarily in patients who are volume-depleted. Hyperkalemia occurs primarily in patients receiving potassium-sparing diuretics or potassium supplements. Cough has been reported frequently in adults.
The CrCl significantly decreased in preterm and term neonates with cardiovascular disease after initiation of ACEIs (captopril or enalapril) in a retrospective review (n=206). The body surface area was less than 0.33 m^2 for all neonates [2].

Solution Compatibility

D_5W, D_5NS, NS, and D_5LR.

Terminal Injection Site Compatibility

Amikacin, aminophylline, ampicillin, aztreonam, calcium gluconate, cefazolin, ceftazidime, chloramphenicol, cimetidine, clindamycin, dobutamine, dopamine, erythromycin lactobionate, esmolol, famotidine, fentanyl, gentamicin, heparin, hydrocortisone succinate, lidocaine, linezolid, magnesium sulfate, meropenem, metronidazole, morphine, nafcillin, nicardipine, nitroprusside, penicillin G, phenobarbital, piperacillin, piperacillin/tazobactam, potassium chloride, propofol, ranitidine, remifentanil, sulfamethoxazole/trimethoprim, tobramycin, and vancomycin.

Terminal Injection Site Incompatibility

Amphotericin B, cefepime, and phenytoin.

Monitoring

Frequent assessment of blood pressure, particularly after the first dose. Periodic assessment of renal function and serum potassium.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Enalaprilat is an ACE inhibitor which blocks the production of the potent vasoconstrictor angiotensin II. It thereby decreases plasma and tissue concentrations of angiotensin II and aldosterone, and increases plasma and tissue renin activity. Enalaprilat also prevents the breakdown of bradykinin, a potent vasodilator. Vascular resistance is reduced without reflex tachycardia. Beneficial effects are thought to be caused by a combination of afterload reduction and long-term inhibition of salt and water retention. Duration of action is quite variable in neonates, ranging from 8 to 24 hours.

ABOUT

Special Considerations/Preparation

Enalaprilat is supplied as a 1.25-mg/mL solution for injection in 1-mL and 2-mL vials. Benzyl alcohol content is 9 mg/mL. To make a dilution for IV use, take 1 mL (1.25 mg) of solution and add 49 mL NS to make a final concentration of 25 mcg/mL (0.025 mg/mL). Dilution stable for 24 hours.

Enoxaparin

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Evaluate all patients for a bleeding disorder before starting treatment, unless treatment is urgently needed[1].

Treatment of Thrombosis:
Term infants: initial, 1.7 mg/kg per dose subQ every 12 hours [2][3].
Preterm infants: initial, 2 mg/kg per dose subQ every 12 hours [2][3].
Adjust dosage to maintain anti-factor X_a level between 0.5 and 1.0 unit/mL. It will usually take several days to attain levels in the target range.
Dosage requirements to maintain target anti-factor X_a levels in preterm infants are quite variable, ranging from 0.8 to 3 mg/kg every 12 hours.

Low-risk prophylaxis: 0.75 mg/kg per dose subQ every 12 hours.
Adjust dosage to maintain anti-factor X_a level between 0.1 and 0.4 units/mL [4][5][6].

Dose Adjustments
Renal Impairment: No dosage adjustment recommendations are available for pediatric patients with renal impairment. However, in adult patients dosages are reduced as follows [1]:
Mild or moderate impairment (CrCl 30 to 80 mL/min): No adjustment necessary [1]
Severe impairment (CrCl less than 30 mL/min)
• **Prophylaxis in abdominal surgery, hip or knee replacement surgery:** 30 mg subQ once daily [1]
• **Prophylaxis in medical patients during acute illness:** 30 mg subQ once daily [1]
Acute DVT, when used in conjunction with warfarin, for either inpatient (with or without pulmonary embolism (PE)) or outpatient (without PE) treatment: 1 mg/kg subQ once daily [1]
• **Prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction (MI), when used in conjunction with aspirin:** 1 mg/kg subQ once daily [1]
• **Acute ST-segment elevation MI (STEMI) in patients younger than 75 years, when used in conjunction with aspirin:** 30 mg single IV bolus dose plus a 1 mg/kg subQ dose followed by 1 mg/kg subQ once daily [1]
A dose reduction of approximately 30% in pediatric patients (older than 1 year) with a creatinine clearance of 30 mL/min/1.73 ^{2} or less was recommended based on a retrospective pharmacokinetic study (n=853) [7].
Hepatic impairment: Studies in patients with hepatic impairment have not been conducted and the impact of hepatic impairment on the exposure to enoxaparin is unknown [1]

Uses

Anticoagulation. Advantages over standard unfractionated heparin:
(1) May be given subcutaneously,
(2) More predictable pharmacokinetics,
(3) Minimal monitoring,
(4) Dosing every 12 hours,
(5) Less frequent bleeding complications. .

One disadvantage is the inability to quickly and completely reverse its anticoagulant effects [9].

Treatment of Thrombosis
Several retrospective studies have suggested that **higher initial doses** are required to more quickly achieve therapeutic anti-Xa levels and reduce the number of dosage adjustments. In a retrospective study (n=33), initial doses of 1.8 +/- 0.4 mg/kg in full-term infants (younger than 2 months) and 2.2 +/- 0.5 mg/kg in preterm infants (37 weeks gestation or less) would have been necessary to achieve therapeutic anti-factor Xa levels [10]. In another retrospective study in children (n=192), higher initial doses (1.7 mg/kg every 12 hours for children 3 months of age and younger; 1.2 mg/kg every 12 hours for children greater than 3 months of age) achieved more rapid therapeutic anti-factor Xa levels resulting in fewer venipunctures, without an increase in adverse events, compared with standard doses. Treatment outcomes (resolution or reduction of thrombus) were not different between groups. The authors concluded a higher starting dose of 1.8 mg/kg every 12 hours for infants less than 3 months of age and 1.5 mg/kg every 12 hours for children 3 to 12 months of age may be considered [11]. A third retrospective study (n=150) found that only 41% of patients attained therapeutic anti-Xa levels with initial dosing consistent with current standard treatment guidelines. The following doses were required to achieve a therapeutic anti-Xa level (dose given every 12 hours): less than one month of age, 1.8 mg/kg; one month to 1 year, 1.64 mg/kg [12]. A fourth retrospective study (n=140) also revealed that less than half of the population achieved therapeutic anti-Xa levels following the initial dose with the current standard treatment guidelines. The following higher doses were required to achieve a therapeutic anti-Xa level (dose given every 12 hours): less than 2 months of age, 1.6 mg/kg; 2 months to 1 year, 1.5 mg/kg [13].

In a retrospective study, whole-milligram enoxaparin dosing **using insulin syringes** (undiluted 100 mg/mL; 1 mg enoxaparin = 0.01 mL = 1 unit) was associated with therapeutic anti-Xa levels and no reported dose measurement errors. The study included neonates, infants and children (n=514); 27% were infants less than 3 months of age (900 to 4700 g in weight). Five children (less than 1%) had a supra-therapeutic initial anti-Xa level without hemorrhagic consequences. No patients needed decimal dosing to attain therapeutic levels [8].

Call 1-800-NOCLOTS for case reporting and treatment guidance.

Administration

Administer by deep subQ injection. **Not for IM administration.**
Insulin syringes have been used to administered enoxaparin (undiluted 100 mg/mL; 1 mg enoxaparin = 0.01 mL = 1 unit) [8].

Administration may be aided by using a small plastic indwelling subcutaneous catheter (Insuflon®, Hypoguard USA). Adverse events related to these catheters are much more frequent in ELBW infants.

MEDICATION SAFETY

Contraindications/Precautions

CONTRAINDICATIONS
•Presence of active major bleeding[18]
• History of immune-mediated heparin-induced thrombocytopenia within the past 100 days or in the presence of circulating antibodies [18].
•Known hypersensitivity to enoxaparin, heparin or pork products, or benzyl alcohol (multidose form contains alcohol)[18]

PRECAUTIONS
Major **bleeding** may occur even with anti-factor Xa levels in the therapeutic range. The overall incidence is approximately 4% in children [6]. Reported complications include major bleeding or hematoma at the administration site, compartment syndrome, intracranial hemorrhage, and gastrointestinal hemorrhage [15][6].
Bleeding can occur at any site [1].
Use with caution in patients with a bleeding diathesis, uncontrolled arterial hypertension or a history of recent gastrointestinal ulceration, diabetic retinopathy, renal dysfunction and hemorrhage [18]
Epidural **hematoma** has been reported in pediatric patients who underwent lumbar puncture while receiving enoxaparin. It is recommended that 2 doses of enoxaparin be held prior to spinal invasive procedures and if possible, anti-Xa levels should be obtained prior to high-risk procedures [19]. Risk of epidural or spinal hemorrhage and subsequent hematomas is increased with the use of postoperative indwelling epidural catheters, with concomitant use of additional drugs affecting hemostasis (e.g. NSAIDs), with traumatic or repeated epidural or spinal puncture, or in patients with a history of spinal surgery or spinal deformity [18]
Heparin-induced thrombocytopenia or heparin-induced thrombocytopenia with thrombosis (HITTS) may occur [1] and was reported (with normal platelet count) in one case study in a child. Although HIT is rare with enoxaparin therapy (less than 1%), children are still at risk for developing it [20]; consider risk/benefit and alternative non-heparin treatment options in patients with history of HIT; monitoring required [1].
Thrombocytopenia of any severity may occur; closely monitor, discontinuation may be required
Serious and fatal adverse events including "gasping syndrome" may occur in neonates and low birth weight infants with use of the multiple-dose vials, which contain **benzyl alcohol**[18].

Adverse Effects

Major and minor bleeds occurred in 4% and 17% of pediatric patients (1 day to 18 years of age (median 3.5 years)) receiving enoxaparin for 146 courses of therapeutic uses and 0% and 6% of 31 pediatric patients (1 week to 17 years of age (median 5.5 years)) receiving prophylactic enoxaparin. Major bleeds were 2 gastrointestinal, 3 (2 of whom were neonates) intracranial bleeds, and 2 thigh hematomas in extremely premature neonates [6].

Black Box Warning

Epidural or spinal hematomas, which may result in long-term or permanent paralysis, may occur in patients who are anticoagulated with low molecular weight heparins or heparinoids and are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing these hematomas include:

- Use of indwelling epidural catheters
- Concomitant use of other drugs that affect hemostasis, such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, and other anticoagulants
- A history of traumatic or repeated epidural or spinal punctures
- A history of spinal deformity or spinal surgery
- Optimal timing between the administration of Lovenox and neuraxial procedures is not known

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary [1].
Consider the benefits and risks before neuroaxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis [1].

Solution Compatibility

NS, D_5W, and sterile water.

Monitoring

Monitor anticoagulant effects using anti-Factor Xa levels if abnormal coagulation parameters or bleeding occur during therapy, or in patients with renal impairment; prothrombin time and aPTT are not adequate for monitoring anticoagulant effects [1].

Measure anti-factor Xa concentrations:

- 4 to 6 hours after a subQ dose - target 0.5 to 1 units/mL
- 2 to 6 hours after a subQ dose - target 0.5 to 0.8 units/mL

. Preterm infants are likely to require several dosage adjustments to achieve the target levels. Obtain anti-factor Xa levels initially, weekly during hospitalization, and then every 3 to 4 weeks in stable patients. After attaining target levels, dosage adjustments will be necessary once or twice a month, perhaps more often in preterm infants and infants with hepatic or renal dysfunction [14][15][9][16]. Anti-factor Xa concentrations vary with the assay method; there is a lack of standardization for methods [17].

Obtain CBC (including platelet count), stool occult blood, and liver function tests during therapy. Monitor blood pressure. Monitor patients with renal impairment closely during therapy (dose reduction necessary). Assess for signs of bleeding and thrombosis. Patients undergoing concomitant neuraxial anesthesia or spinal puncture should be monitored frequently for neurological impairment indicating possible spinal or epidural hematoma [1][14][9][16].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Enoxaparin is a low-molecular weight heparin that has considerably less activity against thrombin than does standard heparin. Efficacy in neonates is decreased due to low antithrombin plasma concentrations. It is also much less likely to interfere with platelet function or cause osteoporosis. It activates antithrombin III, which progressively inactivates both thrombin and factor X_a, key proteolytic enzymes in the formation of fibrinogen and activation of prothrombin. Bioavailability is almost 100% after subcutaneous administration, with peak activity 2.5 to 4 hours later. The apparent half-life of anti-X_a activity is 4 to 5 hours. Clearance in neonates is more rapid than in older infants, children or adults.

ABOUT

Special Considerations/Preparation

Availability: 100-mg/mL concentration as 30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/mL in preservative-free prefilled syringes [18]. Multidose vial available in 100-mg/mL concentration with 15 mg benzyl alcohol per 1 mL as a preservative (not approved for use in neonates or infants) [18].
Undiluted enoxaparin (100 mg/mL) transferred to tuberculin syringes and stored under refrigeration retained anti-Xa activity for 10 days. Syringes stored at room temperature did not retain anti-Xa activity [21].

Enoxaparin Dilution

A 20-mg/mL enoxaparin dilution (in preservative-free sterile water) was stable for 4 weeks in glass vials stored at room temperature. The same dilution was stable in 1-mL tuberculin syringes (6 mg/0.3 mL) for 2 weeks stored at room temperature or under refrigeration. The stability end-point was significant loss of anti-Xa activity; sterility and pyrogenicity tests were not performed [22].

In another stability study, enoxaparin (20 mg/mL in 1-mL tuberculin syringes) diluted in 4% glucose retained greater than 99% of the baseline anti-Xa activity when stored under refrigeration (4 degrees C) for 31 days. A decrease of 10% (statistically significant) of the initial anti-Xa activity was noted when enoxaparin (20 mg/mL in 1 mL tuberculin syringes) was diluted with sterile water and stored under the same conditions. Stability of enoxaparin in commercially available 5% glucose solution was not tested in this study; however, the authors suggest that an increase in glucose concentration would not affect the stability of the dilution [23].

A 20-mg/mL enoxaparin dilution in 0.9% normal saline (in 1-mL polypropylene syringes; 10 mg/0.5 mL) was stable for up to 43 days when stored at room temperature or under refrigeration (2 to 8 degrees C). At least 90% of the baseline anti-Xa activity was retained under these conditions [24].

Enoxaparin 120 mg (1.2 mL) diluted to 100 mL in 0.9% normal saline (1.2 mg/mL final concentration) in polyvinyl chloride containers was stable for up to 48 hours at room temperature; greater than 94% of the baseline anti-Xa activity was retained during the time period [25].

EPINEPHrine (Adrenaline)

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Hypotension or Persistent Bradycardia; Prevention of Cardiac Arrest
Intravenous/Intraosseous (Low-dose): 1 mcg/kg (0.001 mg/kg) IV/IO via central administration for hypotension or persistent bradycardia with a pulse in a patient with an at-risk myocardium [1]; doses were repeated within 5 to 10 minutes and/or alternative therapies started in retrospective pediatric studies [2][3]; may be followed by 0.01 to 0.2 mcg/kg/min [1].

Pulmonary Hemorrhage
Endotracheal: 0.1 mL/kg of a 1:10,000 solution administered via direct endotracheal tube instillation or rapid nebulization [4] OR 0.5 mL of a 1:10,000 solution mixed with 1 mL of air in a 5 mL syringe attached to an orogastric tube; forcefully and quickly inject mixture endotracheally to create a splash [5].

Resuscitation and severe bradycardia:
Intravenous 0.01 to 0.03 mg/kg (10 to 30 mcg/kg) IV with 0.1 mg/mL EPINEPHrine solution . Follow IV administration with 0.5 to 1 mL flush of normal saline [6][7].

IV continuous infusion: Start at 0.1 mcg/kg per minute and adjust to desired response, to a maximum of 1 mcg/kg per minute.
If possible, correct acidosis before administration of EPINEPHrine to enhance the effectiveness of the drug.

Resuscitation and severe bradycardia:
Endotracheal 0.05 to 0.1 mg/kg (50 to 100 mcg/kg) via endotracheal tube with 0.1 mg/mL EPINEPHrine solution. Follow ET administration with several positive pressure ventilations [6][7]. Do **not** administer these higher doses of EPINEPHrine intravenously.
IV route is preferred; safety and efficacy of the endotracheal route has not been evaluated in neonates [6].

Septic Shock; Fluid-Refractory DOPamine-Resistant:
Intravenous 0.05 to 0.3 mcg/kg/min IV [8]

Uses

Acute cardiovascular collapse. Short-term use for treatment of **systemic hypotension**. Despite the widespread use of EPINEPHrine/adrenaline during **resuscitation**, no placebo-controlled studies have evaluated either the tracheal or intravenous administration of EPINEPHrine at any stage during cardiac arrest in human neonates. Nonetheless, it is

reasonable to continue to use EPINEPHrine when adequate ventilation and chest compressions have failed to increase the heart rate to greater than 60 beats per minute [7]. The American Heart Association (AHA) did not review the use of EPINEPHrine in the 2015 Neonatal Resuscitation guidelines; therefore, the 2011 AHA and AAP guidelines still apply [13].
Delayed administration of epinephrine during an in-hospital cardiac arrest with an initial nonshockable rhythm was associated with decreased chance of survival to hospital discharge, decreased chance of return of spontaneous circulation, decreased survival at 24 hours, and decreased survival to hospital discharge with a favorable neurological outcome in a retrospective analysis of registry data (n=1558; median age, 9 months; interquartile range, 13 days to 5 years) [14].

Bronchiolitis: Adrenergic agents are not recommended for the routine treatment of bronchiolitis in infants and children. Although no evidence supports this use, epinephrine as rescue therapy in rapidly deteriorating patients may have potential [15].

Hypotension or Persistent Bradycardia; Prevention of Cardiac Arrest: A pre-arrest small dose may avert cardiac arrest and allow time to treat an acute critical problem or to initiate extracorporeal life support without requiring extracorporeal cardiopulmonary resuscitation for hypotension or persistent bradycardia with a pulse in a patient with an at-risk myocardium [1]. Two retrospective studies demonstrated significant increases in mean arterial blood pressure, systolic blood pressure, and heart rate during acute episodes of hypotension in critically ill children administered low-dose EPINEPHrine boluses [2][3] at median doses of 0.7 mcg/kg IV (interquartile range (IQR) 0.3 to 2 mcg/kg) [3] and 1.3 mcg/kg IV (range, 0.2 to 5 mcg/kg). The median age was 9 years (IQR, 1 to 15 years) in one study (n=19 patients; 24 episodes) [2]. In the other study (n=144), the age groups were younger than 1 year (gestational age 37 weeks or longer) (47%), 1 to 5 years (17%), 5 to younger than 12 years (15%), and 12 to younger than 18 years (22%) [3]. Other terms used for this treatment was low-dose, dwindle dose, push-dose pressor, bolus-dose, spritzer vasopressor, or pre-arrest bolus dilute EPINEPHrine [2][3].

Pulmonary Hemorrhage: Endotracheally administered EPINEPHrine may be effective for the treatment of severe pulmonary hemorrhage as reported in small studies [5][4]. Endotracheally administered EPINEPHrine resolved pulmonary hemorrhage in most cases after 3 to 5 applications in a retrospective study of neonates weighing less than 1500 g with severe pulmonary hemorrhage. Five deaths were reported before discharge; only 1 was due to pulmonary hemorrhage (parents refused further treatment). Mean gestational age was 27 weeks, and mean birth weight was 820 g. EPINEPHrine was sprayed via endotracheal tube (ET) after each ET suction until resolution. EPINEPHrine was sprayed by mixing 0.5 mL of a 1:10,000 solution with 1 mL of air in a 5 mL syringe attached to an orogastric tube; the mixture was then forcefully and quickly injected to create a splash [5].
A retrospective study found no difference in survival rates with mean airway pressure increases alone (n=14) compared with mean airway pressure increases plus endotracheal EPINEPHrine or cocaine (n=28; survival rate 43% for each group). Combination therapy was associated with increases in peak inspiratory pressure (PIP) compared with mean airway pressure increases alone (9.4 cm H_2O vs 2.6 cm H_2O), but not with changes in positive end-expiratory pressure (PEEP) values. Mean gestational age was 28.7 weeks (range, 23 to 41 weeks), mean age at occurrence of pulmonary hemorrhage was 3.1 days (range, 2 hours to 25 days), mean birth weight was 1348 g (range, 410 to 4775 g), and all were given vitamin K at birth. EPINEPHrine dosage was 0.1 mL/kg of a 1:10,000 solution administered via direct

endotracheal tube instillation or rapid nebulization in 1 mL NS in the ventilator circuit. Cocaine dosage was 4 mL/kg of a 4% solution administered via direct endotracheal tube instillation or rapid nebulization in 1 mL NS in the ventilator circuit [4].

Severe Sepsis and Septic Shock[8]

<table>
<tr><td colspan="3">Hemodynamic Support - First 60 Minutes</td></tr>
<tr><td>Time</td><td colspan="2">Management- Proceed to next step if shock persists</td></tr>
<tr><td>0 minutes</td><td colspan="2">Maintain airway and establish access</td></tr>
<tr><td>5 minutes</td><td colspan="2">Push 10 mL/kg isotonic crystalloid or colloid boluses up to 40 mL/kg until improved perfusion or unless hepatomegaly.
Begin prostaglandin infusion until rule out ductal-dependent lesion.</td></tr>
<tr><td rowspan="2">15 minutes</td><td colspan="2">DOPamine less than 10 mcg/kg/min +/- DOBUTamine for fluid-refractory shock</td></tr>
<tr><td colspan="2">EPINEPHrine 0.05 to 0.3 mcg/kg/min for fluid-refractory DOPamine-resistant shock</td></tr>
<tr><td rowspan="4">60 min</td><td>Cold shock-Poor LV function
Normal blood pressure
ScvO(2) less than 70%*/Hgb greater than 12 g/dL
SVC flow less than 40 mL/kg/min or CI less than 3.3 L/min/m(2)</td><td>Add nitrovasodilator milrinone or inamrinone with volume loading</td></tr>
<tr><td>Cold shock- Poor RV function
PPHN
ScvO(2) less than 70%*
SVC flow less than 40 mL/kg/min or CI less than 3.3 L/min/m(2)</td><td>Inhaled nitric oxide
Inhaled iloprost or IV adenosine
IV milrinone or inamrinone</td></tr>
<tr><td>Warm shock- Low blood pressure</td><td>Titrate volume
Add norepinephrine
Vasopressin or terlipressin or angiotensin</td></tr>
<tr><td>Refractory shock</td><td>Hydrocortisone if absolute adrenal insufficiency.
Triiodothyronine if hypothyroid.</td></tr>
</table>

		Begin pentoxifylline if VLBW newborn. Consider closing PDA if hemodynamically significant.
	ECMO	
Goals •First Hour: restore and maintain heart rate thresholds, capillary refill of 2 seconds or less, and normal blood pressure. • NICU: normal MAP-CVP, preductal and postductal oxygen saturation difference less than 5%, *ScvO(2) greater than 70% (except congenital heart patients with mixing lesions), SVC flow greater than 40 mL/kg/min, or cardiac index greater than 3.3 L/min/m(2)		
KEY: CI = cardiac index, Hgb = hemoglobin, LV function = left ventricle function, MAP-CVP = mean arterial pressure-central venous pressure, PDA = patent ductus arteriosus, PPHN = persistent pulmonary hypertension of the newborn, ScvO(2) = continuous central venous oxygen saturation, SVC = superior vena cava, VLBW = very low birth weight		
Davis et al: Crit Care Med 2017;45(6)		

There was no difference between epinephrine and dopamine for fluid-refractory septic shock in a randomized, double-blind controlled trial (n=40) in India; however, the study was underpowered. After persistent shock despite 2 boluses of normal saline 10 mL/kg, epinephrine 0.2 mcg/kg/min or dopamine 10 mcg/kg/min were started. Doses were increased, if needed, after 15 minutes to epinephrine 0.3 mcg/kg/min or dopamine 15 mcg/kg/min; then again, if needed, after another 15 minutes to epinephrine 0.4 mcg/kg/min or dopamine 20 mcg/kg/min. The mean gestational age was 30.3 weeks (1.1 kg birth weight) for epinephrine group and 30.7 weeks (1.181 kg birth weight) for dopamine group [16].

Administration

Intravenous: When giving IV push, follow administration with 0.5 to 1 mL flush of normal saline. Always use the 0.1 mg/mL concentration for individual doses and the 1 mg/mL concentration to prepare continuous infusion solution.
For continuous infusion, 10 mcg/mL is the recommended concentration for neonates [9]. Some institutions use standard concentrations of 10, 16, 20, 32, 40, 50, 60, 64, 100, 200, or 700 mcg/mL for continuous infusions in pediatric patients [10].
Endotracheal: Instill directly into ET tube and follow with several positive-pressure ventilations [7].

Endotracheal spray for pulmonary hemorrhage: EPINEPHrine was sprayed by mixing 0.5 mL of a 1:10,000 solution with 1 mL of air in a 5 mL syringe attached to an orogastric tube; the mixture was then forcefully and quickly injected to create a splash [5].
Endotracheal nebulization for pulmonary hemorrhage: Dilute dose in 1 mL NS and rapidly nebulize in the ventilator circuit [4]

Intravenous infusion:
Solution Preparation Calculations
To calculate the AMOUNT of drug needed per defined final fluid volume:
Desired final concentration (mg/mL) x defined final fluid volume (mL) = AMOUNT of drug to add to final infusion solution (mg).
To calculate the VOLUME of drug needed per defined final fluid volume:
*AMOUNT of drug to add (mg) ÷ drug (vial) concentration (mg/mL) = VOLUME of drug to add (mL)
Example (for EPINEPHrine): Mix 50 mL of 20 mcg/mL solution using EPINEPHrine concentration of 1 mg/mL.
20 mcg/mL = 0.02 mg/mL
0.02 mg/mL × 50 mL = 1 mg EPINEPHrine
***1 mg ÷ 1 mg/mL = 1 mL of EPINEPHrine**
Add 1 mL of EPINEPHrine (1 mg/mL) to 49 mL of compatible solution (eg, D_5 W) to yield 50 mL of infusion solution with a concentration of 20 mcg/mL.
Maximum concentration 60 mcg/mL.

Epinephrine Titration Chart		
Concentration (mcg/mL)	**Dose (mcg/kg/min)**	**IV Rate (mL/kg/hour)**
10	0.05 0.1 0.5 1	0.3 0.6 3 6
20	0.05 0.1 0.5 1	0.15 0.3 1.5 3
30	0.05 0.1 0.5 1	0.1 0.2 1 2
40	0.05 0.1 0.5 1	0.075 0.15 0.75 1.5
50	0.05 0.1 0.5 1	0.06 0.12 0.6 1.2
60	0.05 0.1 0.5 1	0.05 0.1 0.5 1

IV Low-dose EPINEPHrine: Concentrations of 0.01 mg/mL (10 mcg/mL) may be used [2][3][11]; via central administration [1]. Preparation (10 mcg/mL): Draw up 9 mL of normal saline into a 10 mL syringe, then draw up 1 mL of EPINEPHrine 0.1 mg/mL [12].

MEDICATION SAFETY

Adverse Effects

Compared to dopamine, continuous infusions at doses yielding similar changes in blood pressure are more likely to cause hyperglycemia, tachycardia, and elevations in serum lactate. Cardiac arrhythmias (PVCs and ventricular tachycardia) are also more likely. Renal vascular ischemia may occur at higher doses. Bolus doses are associated with severe hypertension and intracranial hemorrhage. Increased myocardial oxygen requirements. IV infiltration may cause tissue ischemia and necrosis. Suggested treatment: Inject a 1 mg/mL solution of phentolamine into the affected area. The usual amount needed is 1 to 5 mL, depending on the size of the infiltrate.

Solution Compatibility

D_5W, $D_{10}W$, and NS. Although NS is compatible, administration in saline solution alone is not recommended. Dextrose protects against oxidation of epinephrine [17].

Terminal Injection Site Compatibility

Amikacin, amiodarone, caffeine citrate, calcium chloride, calcium gluconate, ceftazidime, cimetidine, dobutamine, dopamine, famotidine, fentanyl, furosemide, heparin, hydrocortisone succinate, ibuprofen lysine, lorazepam, midazolam, milrinone, morphine, nicardipine, nitroglycerin, nitroprusside, pancuronium bromide, potassium chloride, propofol, ranitidine, remifentanil, vecuronium, and vitamin K_1.

Terminal Injection Site Incompatibility

Aminophylline, ampicillin, hyaluronidase, micafungin, and sodium bicarbonate.

Monitoring

Monitor heart rate and blood pressure continuously. Observe IV site for signs of infiltration.

For a full-term newborn, the target heart rate and perfusion pressure (mean arterial pressure minus central venous pressure) are 110 to 160 beats/min and 55 mm Hg, respectively [8].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

EPINEPHrine (adrenaline) is the major hormone secreted by the adrenal medulla. It is a potent stimulator of both alpha and beta adrenergic receptors, with complex effects on body organ systems. Low doses are associated with systemic and pulmonary vasodilation. Higher doses increase blood pressure by direct myocardial stimulation, increases in heart rate, and vasoconstriction. Myocardial oxygen consumption is increased. Blood flow to skeletal muscle, brain, liver, and myocardium is increased. However, blood flow to the kidney is decreased due to increased vascular resistance.

ABOUT

Special Considerations/Preparation

Available: 0.1 mg/mL and 1 mg/mL concentrations. **Always use the 0.1 mg/mL concentration for individual doses and the 1 mg/mL concentration to prepare continuous infusion solution.** Protect from light. Store at room temperature. Do not use if solution is discolored or precipitation occurs [17].

Stability of Prepared IV Solutions
EPINEPHrine solutions of **25, 50, 100 mcg/mL** in D5W protected from light in sterile infusion bags (IntraVia container, Baxter) and stored at either 4° or 25° Celsius maintained at least 90% potency for up to 30 days [18].
EPINEPHrine solutions of **20, 300, 900 mcg/mL** in D5W, D10W, or sodium chloride 0.9% in polypropylene syringes (Becton-Deckinson) and stored at 23° Celsius maintained at least 95% potency for at least 84 hours [19].
An EPINEPHrine solution of **100 mcg/mL** in D5W protected from light in polyvinyl chloride minibags and stored at 23° Celsius maintained at least 99% potency for at least 24 hours [20].
An EPINEPHrine solution of **16 mcg/mL** in D5W protected from light in Viaflex bags (Baxter) and stored at 5° Celsius was unstable after 20 days [21].

Some EPINEPHrine formulations contain sodium metabisulfite.

Epoetin alfa

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

200 to 400 units/kg/dose subQ or IV, 3 to 5 times per week, for 2 to 6 weeks.
Total dose **per week** is 600 to 1400 units per kg subQ or IV.

Short course: 300 units/kg/dose daily subQ or IV for 10 days.

Supplemental iron therapy should be initiated concurrently.

Anemia of prematurity: *Neither early* [1]*nor late* [2]*erythropoietin administration provided clinically significant benefit with regard to donor blood exposure in 2 meta-analyses (n=34 studies (3643 preterm and/or low birth weight infants)* [1]*and n=31 studies (1651 preterm infants)).*[3]*Therefore, erythropoietin is not recommended* [1].

Uses

Hypoxic-ischemic Encephalopathy (HIE): Multiple high-doses of erythropoietin resulted in significantly improved short-term (12 months) motor outcomes in one, but not both, neurodevelopment assessment tests in newborns (mean gestational age, 38.7 weeks) undergoing hypothermia for moderate to severe HIE in a phase II double-blind, placebo-controlled trial (n=50). Less MRI brain injury was observed at a mean age of 5.2 days in the erythropoietin group compared with placebo group. Dosage of erythropoietin was 1000 units/kg IV on days 1, 2, 3, 5, and 7 (total, 5 doses) starting within the first 24 hours of life [6]. In term neonates with moderate or severe HIE who received 5 doses of erythropoietin 500 units/kg initiated by 6 hours of age without hypothermia therapy (n=100), composite death or moderate or severe disability at 19 months of age was significantly reduced by 43% (95% CI, 15% to 62%) and survival without neurological abnormality was significantly improved by 35% (95% CI, 6% to 55%; p=0.016) compared with placebo. However, there was no significant difference from placebo for death or disability in those with severe encephalopathy [7].

Neurocognitive Development - Prematurity:
Summary: Erythropoietin may provide a benefit in mental development but not other areas such as cerebral palsy, vision, or hearing in preterm newborns [8][9][10]. The benefit in preterm newborns may be limited to newborns 28 weeks or older gestation [11][8].
•There was no significant difference between high-dose erythropoietin and placebo administered to extremely preterm newborns (24 weeks to 27 weeks 6 days gestation) in the primary outcome of death or severe neurodevelopment impairment at 22 to 26 months postmenstrual age in a double-blind, randomized trial (N=941). The relative risk for severe neurodevelopment impairment was 0.79 (95% CI, 0.51 to 1.22); 11% in the erythropoietin

group and 14% in the placebo group. Severe neurodevelopment was defined as the presence of severe cerebral palsy or a Bayley III Scales of Infant Development motor or cognitive score of less than 70. For moderate neurodevelopment impairment, there was no clinical difference between groups. Adverse events (severe bronchopulmonary dysplasia, medically or surgically treated patent ductus arteriosus, intracranial hemorrhage, necrotizing enterocolitis, and retinopathy of prematurity) were not different between the groups. The dosages of erythropoietin were 1000 units/kg IV every 48 hours for 6 doses, then 400 units/kg subQ 3 times a week through 32 weeks 6 days of postmenstrual age [11].
•In a meta-analysis including 4 randomized studies with 1133 preterm infants, prophylactic erythropoietin significantly reduced the incidence of a mental development index (MDI; Bayley Scales of Infant Development) of less than 70 at 18 to 24 months' corrected age compared with placebo or no treatment (odds ratio, 0.51; 95% CI, 0.31 to 0.81). However, there was no significant difference in psychomotor development index of less than 70, or in development of cerebral palsy, visual impairment, or hearing impairment. With limited data in infants less than 28 weeks' gestation, no significant difference in MDI less than 70 was observed [8]. In one of the included studies that showed no difference in neurodevelopmental outcomes at 2 years' corrected age in infants with a mean gestational age of 29 weeks (n=450), the dosage was erythropoietin 3000 international units/kg/dose (max 4500 international units/dose for weight 1.5 kg or greater) IV within 3 hours, at 12 to 18 hours, and at 36 to 42 hours after birth [12]. Another of the studies included in the meta-analysis showed neurocognitive outcomes that were minimally better in preterm infants treated with erythropoiesis stimulating agents (ESA) (erythropoietin or darbepoetin) compared with placebo, at 18 to 22 months of age (n=80) at high-altitude institutions. The study only used the Bayley Scales of Infant Development III to evaluate the infants. ESAs were continued until 35 weeks' gestation was completed; 400 units/kg/dose subQ 3 times weekly for erythropoietin and 10 mcg/kg/dose subQ once weekly for darbepoetin [9]. At 2.5 to 4 years of age the same children (n=53) had significantly higher cognitive scores and improved executive function in the ESA group compared with placebo. When compared with term infants without complications, the cognitive performance in the ESA group were lower. Dosages were erythropoietin 400 units/kg/dose subQ 3 times a week and darbepoetin 10 mcg/kg/dose subQ once weekly until 35 completed weeks's gestation, discharge, transfer to another hospital, or death [10].

Anemia of prematurity

Early administration (before 8 days of age): Although there was a reduction in the use of RBC transfusions (RR 0.79 (95% CI 0.74 to 0.85)), volume of RBCs transfused, and number of donor exposures, with erythropoiesis-stimulating agents (ESAs; mostly epoetin alfa) compared with placebo, the differences were not clinically significant. This was demonstrated in a meta-analysis (n=34 studies; 3643 preterm and/or very low birthweight infants). ESAs did not have a significant effect on mortality. Retinopathy of prematurity (stage 3 or more) was not different between the 2 groups. There were conflicting results for neuroprotection, neurodevelopmental outcomes, intraventricular hemorrhage (grades III and IV), periventricular leukomalacia, and necrotizing enterocolitis [1].

Late administration: Although, the use of late administration (between 8 to 28 days of age) reduced the number of RBC transfusion per infant (by less than 1 transfusion/infant) the total volume of RBC transfused/infant was not reduced. Furthermore, most infants received blood transfusions prior to erythropoietin administration. Clinically significant adverse outcomes did not increase or decrease with late administration [3].

Administration

• Do not use epoetin alfa from multidose vials in neonates or infants; contains benzyl alcohol. Do not use single-dose vials admixed with bacteriostatic saline containing benzyl alcohol in neonates and infants [4].
• Administer subQ [4] or via IV bolus [5]

MEDICATION SAFETY

Contraindications/Precautions

Contraindicated in patients with a known hypersensitivity to mammalian cell-derived products or albumin (human), patients with uncontrolled hypertension, or in patients with pure red cell aplasia that develops with epoetin or other erythropoietin protein drugs. Multidose vials contains benzyl alcohol; use single-dose vials in neonates.

Benzyl alcohol: Multidose vial contains benzyl alcohol which has been associated with fatal gasping syndrome in neonates and infants [14]
Dermatologic: Blistering and skin exfoliation reactions, including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported; discontinue use immediately if suspected [14]

Adverse Effects

An adverse effect in premature neonates is neutropenia, which occurs rarely and resolves with discontinuation of the drug.
Although data are conflicting, erythropoietin may be associated with retinopathy of prematurity (ROP). The risk may be reduced for stage greater than 3 ROP if erythropoietin is initiated before 8 days of age [15]
Treatment of preterm infants (median gestational age, 29 weeks) with epoetin was associated with an increased risk of infantile hemangiomas in a retrospective study; hazard ratio of 2.82 (n=2563) [16].

Black Box Warning

Adult patients with chronic kidney disease treated with erythropoiesis-stimulating agents (ESAs) to target a hemoglobin levels greater than 11 g/dL had a greater risk of serious cardiovascular reactions, stroke, and death. In addition, ESAs reduced survival and increased the risk of tumor progression or recurrence in studies of adult patients with cancers of the breast, non-small cell lung, head and neck, lymphoid, and cervix. No clinical trial has identified a risk-free hemoglobin target level, ESA dose, or dosing strategy.

The manufacturer recommends the lowest epoetin alpha dose needed to reduce RBC transfusion requirements for both chronic kidney disease and cancer indications. Prescribers and hospitals must enroll in the ESA APPRISE Oncology Program to prescribe and dispense epoetin alpha to patients with cancer. In patients with cancer, use ESAs only to treat anemia associated with myelosuppressive therapy, and discontinue treatment when a chemotherapy course is completed. ESAs are not indicated with myelosuppressive therapy for patients with cancer with a high probability of cure. Due to an increased risk of DVT, presurgical prophylaxis is recommended. These findings have unknown relevance in the neonatal population [13].

Monitoring

Weekly CBC to check for neutropenia and monitor RBC response.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action: Epoetin alfa is a 165-amino acid glycoprotein manufactured by recombinant DNA technology that has the same biological effects as endogenous erythropoietin. It acts on mature erythroid progenitors, CFU-E, by binding to cell surface receptors and stimulating differentiation and cell division. Noticeable effects on hematocrit and reticulocyte counts occur within 2 weeks. Adequate iron and protein intake is necessary for epoetin to be effective (additional Vitamin E intake may be necessary as well).

Subcutaneously administered drug appears to be pharmacodynamically as effective as IV, despite only 40% bioavailability. Half-life of r-HuEPO in preterm infants is approximately 12 hours. Doses reported in the literature are all stated as units/kg **per week**. Efficacy may be dose dependent in the range of 500 to 1500 units/kg per week (see meta-analysis by Garcia et al), but no differences were observed in the randomized trial by Maier et al.
Hypoxic-ischemic Encephalopathy (HIE) treated with hypothermia: Target neuroprotective $AUC_{48\ hours}$ of 140,000 milliUnits x hr/mL was achieved in all neonates (36 weeks' gestational age or older) receiving erythropoietin 1000 units/kg every 24 hours for 3 doses followed by every 48 hours for 2 doses (n=23), but in none of those who received a dose of 1000 units/kg every 48 hours to a maximum of 6 doses (n=7). For a typical 3.4 kg neonate receiving hypothermia, clearance was estimated at 0.0289 (standard error, 4.5%) L/hr and Vd of the central and peripheral compartments at 0.25 (4.1%) and 0.326 L (10.9%) [17].

ABOUT

Special Considerations/Preparation

Available in preservative-free, single-use, 1-mL vials containing 2000, 3000, 4000, or 10,000 units formulated in an isotonic, sodium chloride/sodium citrate buffered solution with 2.5 mg human albumin. Store refrigerated at 2 to 8 degrees C (36 to 46 degrees F). **Do not freeze or shake.** Undiluted epoetin is stable in plastic syringes for 2 weeks. For IV infusion, dilute epoetin in 2 mL of solutions containing at least 0.05% protein and infuse over 4 hours. These dilutions are stable for 24 hours. Product support for use in neonates is handled by Ortho Biotech, Inc. (Procrit®). Multidose 1-mL (20,000 units/mL) and 2-mL (10,000 units/mL) vials are also available from both Ortho Biotech (Procrit®) and Amgen (Epogen®) containing 1% (10 mg/mL) benzyl alcohol solution with 2.5-mg albumin per mL. Discard multidose vials 21 days after initial entry.

Enrollment in the ESA APPRISE Oncology program is required to prescribe and dispense epoetin alpha to patients with cancer and anemia due to myelosuppressive chemotherapy (www.esa-apprise.com or 1-866-284-8089). Both prescribers and patients must acknowledge the risks of epoetin alpha treatment in writing before initiation of each new course of therapy [18].

Erythromycin

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

KIDs List: Avoid oral and IV use in neonates (unless treating Chlamydia trachomatis pneumonia) due to risk of hypertrophic pyloric stenosis [1].
Oral

Pneumonitis and conjunctivitis due to Chlamydia trachomatis: 12.5 mg/kg per dose orally every 6 hours for 14 days [2].

Pertussis, treatment and prophylaxis: 12.5 mg/kg per dose orally every 6 hours for 14 days. The drug of choice in infants younger than 1 month of age is azithromycin. Administer with infant formula to enhance absorption of the ethylsuccinate and reduce possible GI side effects.

Feeding intolerance due to dysmotility: 40 to 50 mg/kg/day orally in divided doses; may be most effective in neonates with gestational age 32 weeks or greater [3]

Other infections and prophylaxis: 10 mg/kg per dose orally every 6 hours.

Intravenous
Severe infections when oral route unavailable: 5 to 10 mg/kg per dose IV infusion by syringe pump over at least 60 minutes every 6 hours.
Do not administer IM.

Ophthalmic
Prophylaxis of gonococcal ophthalmia neonatorum: Ribbon of 0.5% ointment instilled in each conjunctival sac [4][2].

Uses

General: Treatment of infections caused by *Chlamydia, Mycoplasma,* and *Ureaplasma.* Treatment for and prophylaxis against *Bordetella pertussis.* As a substitute for penicillin in situations of significant allergic intolerance. As a prokinetic agent in cases of feeding intolerance.

Chlamydial Infection: Oral erythromycin base or erythromycin ethylsuccinate is recommended as the first-line agent for the treatment of ophthalmia neonatorum or pneumonia caused by *Chlamydia trachomatis* [2].

Gonococcal Ophthalmia Neonatorum; Prophylaxis: Universal prophylaxis with

ophthalmic erythromycin to all newborns, regardless of gestational age, is recommended to prevent gonococcal ophthalmia neonatorum [4].

Feeding intolerance: A systematic review reported mixed results on the efficacy of erythromycin compared with placebo to prevent or treat feeding intolerance in preterm neonates (10 studies; 7 treatment, 3 prevention). A meta-analysis was unable to be performed on the primary outcome of time to achieve full enteral feeding due to significant heterogeneity between studies. Four studies (1 prevention, 3 treatment) used lower erythromycin doses (12 mg/kg/day or less) while the other studies used higher doses (greater than 12 mg/kg/day). It was noted that 3 of the high-dose studies (40 to 50 mg/kg/day) reported significant results in favor of erythromycin. Two studies each performed a subgroup analysis based on gestational age and both found significant results favoring erythromycin in those with a gestational age 32 weeks or older, but not in those with a gestational age less than 32 weeks [3]. This correlates with previous studies showing propagation of phase III migrating motor complex activity is underdeveloped in neonates with a gestational age less than 32 weeks [6]. The number of necrotizing enterocolitis cases was not significantly different between groups, and no cases of hypertrophic pyloric stenosis were reported in any of the studies [3].

Administration

Intravenous: Give as intermittent infusion over at least 60 minutes at a concentration of 1 to 5 mg/mL. IV push administration is not recommended [5].

MEDICATION SAFETY

Contraindications/Precautions

Contraindications
Concomitant use with astemizole, terfenadine, cisapride, pimozide, ergotamine, or dihydroergotamine [7]
Concomitant use with HMG CoA reductase inhibitors (statins) that are extensively metabolized by CYP3A4 (lovastatin or simvastatin) [8]

Precautions
Cardiovascular: Life-threatening episodes of ventricular tachycardia associated with prolonged QT intervals (torsades de pointes) have been reported; increased risk in patients with electrolyte imbalance, hepatic dysfunction, myocardial ischemia, left ventricular dysfunction, idiopathic QT prolongation, and concurrent antiarrhythmic treatment [7].
Cardiovascular: QT interval prolongation, including rare cases of arrhythmia, torsade de pointes, and fatalities, has been reported; avoid use with known QT prolongation, uncorrected hypokalemia or hypomagnesemia, clinically significant bradycardia, and with Class IA (quinidine, procainamide), or Class III (dofetilide, amiodarone, sotalol) antiarrhythmic agents [9]

Gastrointestinal: Clostridium difficile associated diarrhea (CDAD) has been reported; may range in severity from mild diarrhea to fatal colitis. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against C. difficile may need to be discontinued; initiate appropriate fluid/electrolyte management, protein supplementation, antibacterial drug treatment for C difficile, and surgical evaluation if clinically indicated [7].
Gastrointestinal: Infantile hypertrophic pyloric stenosis (IHPS) has been reported in infants following erythromycin treatment; weigh benefits against potential risk of developing IHPS [7]
Hepatic: Hepatic dysfunction, with or without jaundice, has been reported with oral erythromycin products; monitoring recommended for patients with impaired liver function [7]
Immunologic: Superinfection may occur with prolonged or repeated use; discontinue treatment and institute appropriate therapy [7]
Musculoskeletal: Exacerbation of weakness in patients with myasthenia gravis has been reported [7]

Adverse Effects

The use of macrolide antibiotics was associated with infantile hypertrophic pyloric stenosis with a 30-fold increased risk in infants exposed at 0 to 13 days of age and 3-fold increased risk in infants exposed at 14 to 120 days of age in an observational study (n=6591) [10]. Similar outcomes (highest risk of pyloric stenosis when exposed within the first couple weeks of life; although risk still present at 6 weeks of life) were demonstrated in another observational study (n=1902 exposed to erythromycin) [11].
Two reported cases of severe bradycardia and hypotension occurring during IV administration of erythromycin lactobionate. Intrahepatic cholestasis. Loose stools occur infrequently. Bilateral sensorineural hearing loss has been reported rarely in adults, usually associated with IV administration and renal or hepatic dysfunction. The hearing loss occurred after the first few doses and was reversible after discontinuing the drug. Venous irritation is common when using the IV dosage form.

Solution Compatibility

NS and sterile water for injection.

Solution Incompatibility

D_5W and $D_{10}W$ (unless buffered with 4% sodium bicarbonate to maintain stability).

Terminal Injection Site Compatibility

Acyclovir, aminophylline, amiodarone, cimetidine, enalaprilat, esmolol, famotidine, heparin, hydrocortisone succinate, lidocaine, lorazepam, magnesium sulfate, midazolam, morphine, nicardipine, penicillin G, pentobarbital, potassium chloride, ranitidine, sodium bicarbonate, and zidovudine.

Terminal Injection Site Incompatibility

Ampicillin, cefepime, cefotaxime, ceftazidime, chloramphenicol, fluconazole, furosemide, linezolid, and metoclopramide.

Monitoring

Watch for diarrhea and signs of abdominal discomfort. CBC for eosinophilia. **Monitor heart rate and blood pressure closely during IV administration.** Observe IV site for signs of infiltration.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action: Erythromycin may be bacteriostatic or bactericidal depending on the tissue concentration of drug and the microorganism involved. The drug penetrates poorly into the CNS, is concentrated in the liver, and is excreted in the bile [5][12].

Pharmacokinetics
IV administration of E. lactobionate to preterm infants, using doses of 6.25 to 10 mg/kg, yielded peak serum concentrations of 1.9 to 3.7 mcg/mL and a half-life of 2 hours. The drug penetrates poorly into the CNS, is concentrated in the liver and bile, and is excreted via the bowel. It is a motilin receptor agonist and induces stomach and small intestine motor activity. Plasma clearance of midazolam is reduced by 50%. Digoxin, midazolam, theophylline and carbamazepine serum concentrations may be significantly increased because of prolongation of their half-life.

ABOUT

Special Considerations/Preparation

Oral: Erythromycin ethylsuccinate oral suspension is available in concentrations of 200 mg/5

mL (40 mg/mL) and 400 mg/5 mL (80 mg/mL). Refrigeration not required except to preserve taste. Shake suspension well before administering. To prepare a 20 mg/mL dilution of the oral suspension, dilute 5 mL of the 200 mg/5 mL (40 mg/mL) erythromycin ethylsuccinate suspension (suspension made from powder for suspension only) up to a final volume of 10 mL with sterile water. Erythromycin ethylsuccinate suspension made from powder for suspension, at usual concentrations of 40 mg/mL and 80 mg/mL, is stable for 35 days at room temperature.

Injection: Available as powder for injection in 500-mg and 1-g vials. Reconstitute 500-mg vial with 10 mL of sterile water for injection to concentration of 50 mg/mL. Reconstituted solution stable for 24 hours at room temperature or 2 weeks in refrigerator. After reconstitution, dilute to a concentration of 1 to 5 mg/mL for infusion. To make a 5-mg/mL dilution, add 1 mL of reconstituted solution to 9 mL sterile water for injection. Use diluted drug within 8 hours [5].

Ophthalmic: Erythromycin ophthalmic is available as a 0.5% ointment.

Esmolol

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Supraventricular tachycardia (SVT):
Loading dose: 100 to 500 mcg/kg IV over 1 minute [1]
Maintenance dose: 25 to 100 mcg/kg/min continuous IV infusion, titrated by 25 to 50 mcg/kg/min increments up to 500 mcg/kg/min [1]

Acute management of hypertension, post cardiovascular surgery
Study dosage: 125 mcg/kg IV bolus followed by 125 mcg/kg/min continuous IV infusion, OR 250 mcg/kg IV bolus followed by 250 mcg/kg/min continuous IV infusion, OR 500 mcg/kg IV bolus followed by 500 mcg/kg/min continuous IV infusion. No differences in efficacy or adverse effects was reported between the 3 dose regimens [2].
Alternative dosage: These regimens were suggested by one study, though clinical data is not available for these dosages.
0 to 7 days of age: Initial infusion, 50 mcg/kg/min IV; titrate by 25 to 50 mcg/kg/min every 20 minutes until SBP is 87 mmHG or lower. MAX infusion rate, 1000 mcg/kg/min [3]
8 days to 1 month of age: Initial infusion, 75 mcg/kg/min IV; titrate by 50 mcg/kg/min every 20 minutes until SBP is 101 mmHg or lower. MAX infusion rate, 1000 mcg/kg/min [3]

Uses

Short term treatment of postoperative hypertension, supraventricular tachycardia (SVT), and ventricular tachycardia (VT).

Administration

Iso-osmotic solutions of esmolol are available as 10 mg/mL and 20 mg/mL [4].

MEDICATION SAFETY

Contraindications/Precautions

Contraindications: Sinus bradycardia, heart block greater than first degree, cardiogenic shock or overt heart failure [5]

Adverse Effects

May cause hypotension in high doses. Adverse effects reversible with discontinuation of drug. Monitor IV site closely for vein irritation and phlebitis, especially at high concentrations (greater than 10 mg/mL).

Solution Compatibility

D_5W, LR, D_5LR, NS, ½ NS, D_5 ½ NS, and D_5NS.

Terminal Injection Site Compatibility

Amikacin, aminophylline, atracurium, calcium chloride, cefazolin, ceftazidime, chloramphenicol, cimetidine, clindamycin, dopamine, enalaprilat, erythromycin lactobionate, famotidine, fentanyl, gentamicin, heparin, hydrocortisone, insulin, linezolid, magnesium sulfate, metronidazole, micafungin, midazolam, morphine, nafcillin, nicardipine, nitroglycerin, norepinephrine, pancuronium, penicillin G, phenytoin, piperacillin, potassium chloride, propofol, ranitidine, remifentanil, sodium nitroprusside, tobramycin, trimethoprim/sulfamethoxazole, vancomycin, and vecuronium.

Terminal Injection Site Incompatibility

Amphotericin B, diazepam, furosemide, procainamide, and sodium bicarbonate 5% injection.

Monitoring

Continuous EKG monitoring during acute treatment of arrhythmias. Measure systemic blood pressure and heart rate frequently.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of Action

Esmolol, a short-acting cardioselective adrenergic receptor blocker, exerts selective inhibitory effects on $beta_1$ receptors primarily found in the myocardium. At higher doses, it inhibits $beta_2$ receptors located in the musculature of the bronchi and blood vessels [6].

Pharmacodynamics

Onset of action: 2 to 10 minutes [1]. A bolus dose plus continuous infusion results in achievement of 90% beta blockade at 5 minutes [7].

Duration: 10 to 30 minutes after discontinuation of infusion [1][7]; may last longer with extended use and cumulative doses [1].[6]

Distribution

Protein binding: 55% [8][9][10]

Metabolism

Hydrolysis primarily via red blood cell esterases[6]

Excretion

Renal: 73% to 88% as metabolites, less than 2% as unchanged drug [6]

Clearance: 281 mL/kg/min in newborns and infants, compared with 126 mL/kg/min for children 1 year or older [2]

Half-life: 0.2 to 4.8 minutes in studies including newborns [1]

ABOUT

Special Considerations/Preparation

Esmolol is supplied in preservative-free 10-mL (10 mg/mL) vials, and 2500 mg/250 mL and 2000 mg/100 mL ready-to-use premixed bags. The pH is approximately 4.5 to 5.5. Osmolarity is 312 mOsm/L. Store at room temperature. Stable for at least 24 hours at room temperature or refrigeration when diluted in compatible solutions to a concentration of 10 mg/mL [5].

Factor IX (Recombinant), Fc Fusion Protein

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Hemophilia B

Dose and duration of treatment depend on severity of deficiency, location and extent of bleeding, patient's pharmacokinetic profile, and clinical condition of the patient [1].

On average, one international unit per kg increases the circulating level of Factor IX by approximately 0.6% (international units/dL) in children younger than 6 years [1].

Estimate the required dose or the expected in vivo peak increase in Factor IX level using the following 2 formulas [2]:

- International units/dL (or % of normal) = [Total Dose (international unit/body weight (kg)] X Recovery (international units/dL per international unit/kg)
- OR
- Dose (international units) = Body Weight (kg) X Desired Factor IX Rise (international units/dL or, % of normal) X Reciprocal of Recovery (international units/kg per international units/dL)

Dosing for On-demand Treatment and Control of Bleeding Episodes, Perioperative Management, and Routine Bleeding Prophylaxis		
Bleeding Episodes, On-demand Treatment and Control		
Type of Bleeding	Circulating Factor IX Level Required (international units/dL or % of normal)	Dosing Interval (hours)
Minor and Moderate (eg, uncomplicated hemarthroses, superficial muscle (except iliopsoas) without neurovascular compromise, superficial soft tissue, mucous membranes)	30 to 60	Repeat every 48 hours if there is further evidence of bleeding.
Major	80 to 100	Consider a repeat dose

(eg, iliopsoas and deep muscle with neurovascular injury, or substantial blood loss; pharyngeal, retropharyngeal, retroperitoneal, CNS)		after 6 to 10 hours, and then every 24 hours for the first 3 days. Due to the long half-life, the dose may be reduced and frequency of dosing may be extended after 3 days to every 48 hours or longer until bleeding stops and healing is achieved.
Perioperative Management		
Type of Bleeding	Circulating Factor IX Level Required (international units/dL or % of normal)	Dosing Interval (hours)
Minor (including uncomplicated dental extractions)	50 to 80	A single infusion may be sufficient. Repeat as needed after 24 to 48 hours until bleeding stops and healing is achieved.
Major	60 to 100 (initial level)	Consider a repeat dose after 6 to 10 hours, and then every 24 hours for the first 3 days. Due to the long half-life, the dose may be reduced and frequency

		of dosing may be extended after 3 days to every 48 hours or longer until bleeding stops and healing is achieved.
Routine Bleeding Prophylaxis		
Starting Dose (12 years or older)		
50 international units/kg once weekly or 100 international units/kg once every 10 days		
Starting Dose (younger than 12 years)		
60 international units/kg once weekly		
Reference: Alprolix™ PI, 2017		

Each vial label states the factor IX potency in international units, which is assigned using an in vitro aPTT-based, 1-stage clotting assay calibrated against the WHO international standard for factor IX concentrates. Factor IX activity measurements may be affected by the type of reagent or reference standard used[2].

Uses

Hemophilia B (congenital factor IX deficiency)

Bleeding episodes, control and prevention: Control of bleeding was achieved with 1 dose of coagulation factor IX Fc fusion protein recombinant in the majority of patients with factor IX deficiency for prophylaxis and management of bleeding episodes. Patients with severe factor IX deficiency (age range, 12 to 71 years old; n=123) were evaluated in trials for 2 prophylactic treatment regimens (fixed weekly and individualized interval prophylaxis) and an episodic (ie, on-demand) treatment, and to determine hemostatic efficacy of coagulation factor IX Fc fusion protein recombinant for bleeding episodes and perioperatively in major surgery. In the fixed interval prophylaxis arm, patients received an initial dose of 50 international units/kg, which was then dose adjusted to maintain a factor IX trough of at least 1% to 3% above baseline (median study dose, 45.2 international units/kg). Patients in the individualized interval arm received factor IX Fc fusion protein recombinant 100 international units/kg every 10 days, with the dosing interval adjusted to maintain a factor IX trough of at least 1% to 3% greater than baseline as clinically indicated (median dosing interval, 12.5 days). Patients in the episodic treatment arm received therapy only as needed. Across all groups, 636 bleeding episodes were assessed in 114 patients, who received a median total dose per bleeding episode of 46.99 international units/kg. Most patients were treated with 1 dose (90.4%); 6.9% of patients required 2 doses, and 2.7% required 3 doses. At 8 to 12 hours after treatment, 83.7% of patients treated with 1 dose had excellent or good response, 14.7% had moderate response, and 1.6% had no response. [2].

Bleeding, prophylaxis: In patients with factor IX deficiency, overall annualized bleeding rates were lower in fixed weekly and individualized weekly prophylaxis groups compared with an episodic (ie, on-demand) treatment group in a small study (n=123; 12 to 71 years of age). In the fixed-interval prophylaxis arm, patients received an initial dose of 50 international units/kg, which was then adjusted to maintain a factor IX trough level of at least 1% to 3% above baseline (median dose, 45.2 international units/kg). Patients in the individualized interval arm received factor IX Fc fusion protein recombinant 100 international units/kg every 10 days, with the dosing interval adjusted to maintain a factor IX trough of at least 1% to 3% greater than baseline as clinically indicated (median dosing interval, 12.5 days). Patients in the episodic treatment arm received therapy only as needed. Across all treatment groups, 636 bleeding episodes were assessed in 114 patients, who received a median total dose of 46.99 international units per bleeding episode. During a median followup of 51.4 weeks, the annualized bleeding rates were decreased by 83% in the fixed-weekly interval group and 87% in the individualized group compared with the episodic treatment group. The median annualized overall bleeding rates were 2.95% in the fixed prophylaxis group, 1.38% in the individualized prophylaxis group, and 17.69% in the episodic treatment group [2].

Perioperative Management: In 14 major surgeries (eg, knee replacement, abdominal surgery, complex dental procedure) in patients with factor IX deficiency, hemostatic response of coagulation factor IX Fc fusion protein recombinant was rated as excellent (n=13) or good (n=1) in all patients, 24 hours after surgery There were 15 minor surgical procedures in 13 subjects, all without thrombotic events [2].

FDA approved indication

Coagulation Factor IX Fc fusion protein is indicated for perioperative management, on-demand treatment and control of bleeding episodes, and routine prophylaxis to decrease the frequency of bleeding episodes in adults and children with hemophilia B (congenital factor IX deficiency). The product is not indicated for induction of immune tolerance in patients with hemophilia B [1].

Administration

Allow vial and prefilled diluent syringe to reach room temperature. Using the vial adapter, slowly inject **all** the diluent provided into the drug vial and gently swirl until completely dissolved; do not shake vial. Then turn vial upside down and draw entire vial content into syringe. Following reconstitution, do not refrigerate, protect from direct sunlight, and use within 3 hours. The actual factor IX potency is stated on each vial, but the range is approximately 250, 500, 1000, 2000, 3000, or 4000 international units/vial. When reconstituted with the 5-mL syringe [1], the concentration will approximately range from 50 to 800 international units/mL.

For IV use only. Administer as an IV bolus no faster than 10 mL per minute, according to patient comfort level. Do not administer in the same tubing or container with other drugs [2].

MEDICATION SAFETY

Contraindications/Precautions

Contraindications
•Known hypersensitivity to product or its excipients including sucrose, mannitol, sodium chloride, L-histidine, and polysorbate 20 [1].
Precautions
Hematologic: Thromboembolic complications may occur; increased risk with continuous infusion through central venous catheter; administer as a bolus infusion over several minutes [1]
Immunologic: Hypersensitivity reactions, including anaphylaxis, have been reported; increased risk with the presence of neutralizing antibodies to Factor IX; monitoring recommended; discontinue use if hypersensitivity occurs [1]
Immunologic: Neutralizing antibody formation has been reported; monitoring recommended [1]
Renal: Nephrotic syndrome has been reported following attempted immune tolerance induction in hemophilia B patients with Factor IX inhibitors and a history of allergic reactions to Factor IX [3].

Adverse Effects

The most common adverse effects during clinical trials (n=153) were headache, oral paresthesia, and obstructive uropathy, reported in 1.3% each. Dizziness, dysgeusia, breath odor, fatigue, infusion site pain, palpitations, hematuria, renal colic, hypotension, and decreased appetite were reported in 0.7% each [1].

Monitoring

Monitor plasma factor IX activity, using a one-stage clotting assay, to confirm adequate factor IX levels have been achieved and maintained. The type of aPTT reagent used will affect the factor IX results. An underestimation of activity level will occur if a kaolin-based aPTT reagent is used in the one-stage clotting assay [2].

Regularly monitor for the development of neutralizing antibodies (inhibitors) to factors IX using the Bethesda assay. Furthermore, monitor for antibodies if the expected factor IX activity levels in plasma are not attained or if bleeding is not controlled with the recommended dose. Closely observe for signs and symptoms of acute hypersensitivity reactions, particularly during the early phases of exposure to factor IX [2].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Fully recombinant, fusion protein which temporarily replaces the missing coagulation Factor IX required for effective hemostasis. Provides the Fc region of human IgG_1, which binds to the neonatal FC receptor (FcRn), thereby delaying lysosomal degradation of immunoglobulins by cycling them back into circulation. Incremental recovery is lower and body weight-adjusted clearance is higher in children younger than 12 years compared with adults, particularly in those younger than 6 years. The following table provides pediatric pharmacokinetic parameters [1].

Comparison of Pharmacokinetic Parameters by Age				
Pharmacokinetic Parameter	2 to 5 years (n=11) *	6 to 10 years (n=13) *	12 to 17 years (n=8) *	12 to 17 years (n=3) **
Cmax (international units/dL)	30	37	43	96
Incremental recovery (international units/dL per international units/kg)	0.6	0.74	0.87	0.96
AUC(infinity) (international units X hr/dL)	1169	1471	1439	3420
Half-life (hours)	68	72	80	94
Mean residence time (hours)	86	84	95	95
Clearance (mL/hr/kg)	4.4	3.6	3.7	3
Vd at steady state (mL/kg)	373	302	345	275
* Dose of 50 international units/kg				
** Dose of 100 international units/kg				
Reference: Alprolix™ PI, 2017				

ABOUT

Special Considerations/Preparation

Available: Lyophilized powder in single-use vials containing nominally 250, 500, 1000, 2000,

3000, or 4000 international units and a prefilled diluent 5-mL syringe. The actual factor IX potency is stated on each vial.
Storage: Refrigerate at 2 to 8 degrees C (36 to 46 degrees F); do not freeze. May also store unreconstituted product at room temperature (do not exceed 30 degrees C or 86 degrees F) for a single period of 6 months; discard after this 6-month period. Do not place carton back into refrigeration after warming to room temperature. *Reconstituted product* may be stored at room temperature, not to exceed 30 degrees C (86 degrees F) for up to 3 hours, protect from direct sunlight, and discard any unused product [1].

Factor VIIa, recombinant

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Congenital Hemophilia A or B with inhibitors:
Acute bleeding episode
Hemostatic: 90 mcg/kg IV every 2 hours until hemostasis is achieved or treatment failure; dosage may be adjusted based on severity of bleed [1]; however, higher initial doses (120 mcg/kg) may be necessary in children [2].
Post-Hemostatic (severe bleeds): 90 mcg/kg every 3 to 6 hours to maintain hemostasis. Duration of treatment is unknown [1].
Perioperative management: 90 mcg/kg IV immediately before surgery and every 2 hours during surgery; followed by 90 mcg/kg IV every 2 hours for 48 hours then every 2 to 6 hours until healing occurs for *minor* surgery. Following *major* surgery, dose every 2 hours for 5 days then every 4 hours until healing occurs. Administer additional boluses if needed [1].

Congenital Factor VII Deficiency
Acute bleeding episode: 15 to 30 mcg/kg IV every 4 to 6 hours until hemostasis is achieved. Adjust dose to the individual needs of the patient. Doses as low as 10 mcg/kg have been effective [1].
Perioperative management: 15 to 30 mcg/kg IV immediately before surgery and every 4 to 6 hours during surgery until hemostasis is achieved. Adjust dose to the individual needs of the patient. Doses as low as 10 mcg/kg have been effective [1].

Glanzmann's Thrombasthenia
Acute bleeding episode: 90 mcg/kg IV every 2 to 6 hours until hemostasis is achieved [1].
Perioperative management: 90 mcg/kg IV immediately before surgery and every 2 hours during the procedure, then every 2 to 6 hours following surgery. A median dose of 100 mcg/kg (interquartile range 90 to 140 mcg/kg) has been used in surgical patients who had clinical refractoriness with or without platelet-specific antibodies compared with those with neither [1].

Uses

Cardiac surgery in non-hemophiliacs: There is a lack of evidence to support the use of recombinant coagulation factor VIIa as prophylactic or routine use in non-hemophiliac pediatric patients undergoing cardiac surgery. Although the data are mostly observational [3][4][5], the benefits may outweigh the risk as rescue therapy for refractory blood loss in pediatric patients undergoing cardiac surgery [6][4]. Doses have varied but if recombinant factor VIIa is used the Congenital Cardiac Anesthesia Society Task Force recommends 90 mcg/kg every 2 hours for a maximum of 2 doses based on adult and pediatric clinical studies and pharmacokinetic studies. However, larger doses may be necessary in neonates and

infants due to increased volume of distribution [4].

Other uses in non-hemophiliacs: Factor VIIa has been used in non-hemophiliac pediatric patients for coagulopathies or hemorrhage primarily during cardiac surgery or liver transplantation. Recombinant factor VIIIa has also been used for hemorrhage in pediatric patients with chronic liver disease or failure, disseminated intravascular coagulation, trauma, intracranial hemorrhage, and bleeding associated with malignancy and prophylaxis prior to invasive procedures. Data are limited to small controlled or observational studies; therefore, the evidence for safety and efficacy are inconclusive [3][5].

FDA approved indication
Recombinant Factor VIIa is indicated for perioperative management treatment of bleeding episodes in children with hemophilia A or B with inhibitors, and congenital factor VII deficiency. For Glanzmann's thrombasthenia with refractoriness to platelet transfusions (with or without antibodies to platelets); platelet transfusions are the primary treatment but recombinant factor VIIa is used in severe bleeding episodes requiring systemic hemostatic therapy until hemostasis is achieved and for perioperative management [1].

Administration

Administer 1000 mcg/mL solution as an IV bolus over 2 to 5 minutes, depending on the dose administered. Flush line with 0.9% sodium chloride before or after injection (if needed). Do not mix with other infusion solutions [1].

MEDICATION SAFETY

Contraindications/Precautions

Precautions
Serious arterial and venous thrombotic events, including a fatal event, have been reported and caution is advised in patients at increased risk of thromboembolic events or complications (DIC or history of DIC, crush injury, concomitant treatment with activated or nonactivated prothrombin complex concentrates (aPCCs/PCCs), liver disease, postoperative immobilization, and septicemia) [1]. Furthermore, caution is advised when using higher doses and when used concomitantly with other coagulants [5]. Neonates in general are at risk for thromboembolic complications. Dose reduction or discontinuation may be necessary [1].
Hypersensitivity reactions, including anaphylaxis, have been reported. Administer only if clearly needed to patients with history of known hypersensitivity to recombinant coagulation factor VIIa, any of the product components, or to mouse, hamster, or bovine proteins. Discontinue if symptoms occur, administer appropriate treatment, and weigh benefit and risks before restarting therapy [1].
Factor VII antibodies may develop leading to ineffectiveness or reduced effectiveness [1].

Adverse Effects

Thrombotic events are the most common and serious adverse reactions [1]; However, no thromboembolic events were observed in 29 neonates with intractable bleeding who were administered recombinant factor VIIa at a dose of 100 mcg/kg every 4 hours (maximum 23 doses) [7]. Furthermore, a retrospective study (n=134) of non-hemophilic, non-congenital factor VII deficient neonates demonstrated no increased risk of thrombosis or ischemic events when administered recombinant factor VIIa and other blood products (7.5%) compared with fresh frozen plasma alone (7%) [8].

Black Box Warning

Serious arterial and venous thrombotic events following administration of recombinant factor VIIa have been reported [1]

Monitoring

Monitor prothrombin time and factor VII coagulant activity prior to and following administration in factor VII deficient patients. Evaluate for antibodies if expected levels are not reached, prothrombin time is not corrected, or bleeding is uncontrolled [1].
Evaluate hemostasis as indicator of efficacy and to determine treatment schedule; coagulation parameters do not necessarily correlate with or predict effectiveness [1].
Monitor for signs or symptoms of thrombosis or activation of the coagulation system [1].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

When complexed with tissue factor, coagulation factor VIIa activates coagulation factor X to factor Xa and coagulation factor IX to factor IXa. This process converts prothrombin to thrombin, leading to the formation of a hemostatic plug by converting fibrinogen to fibrin and thereby inducing local hemostasis [1].

ABOUT

Special Considerations/Preparation

Available as lyophilized powder in single use vials containing 1, 2, 5, or 8 mg of recombinant coagulation factor VIIa per vial and a L-histidine (10 mmol) in water diluent as a vial or prefilled syringe [1].
Prior to reconstitution, store between 2 and 25 degrees C (36 and 77 degrees F); protect from freezing and light. Do not use past expiration date [1].
Preparation: Allow recombinant factor VIIa and histidine diluent to reach room temperature. Add appropriate volume of diluent to the vial of lyophilized powder (see below). Do not inject the diluent directly onto the powder. Aim the needle towards the side of the vial so the liquid streams down vial wall. Gently swirl the vial until the powder is dissolved. Do not freeze. Do not store in syringes. May be stored at either room temperature or refrigerated. Use product within 3 hours of reconstitution [1]:

- **Vials**
- 1.1 mL histidine diluent + 1000 mcg vial
- 2.1 mL histidine diluent + 2000 mcg vial
- 5.2 mL histidine diluent + 5000 mcg vial
- 8.1 mL histidine diluent + 8000 mcg vial
- **Pre-filled histidine diluent syringe + Vial of powder**
- 1 mL histidine diluent + 1000 mcg vial
- 2 mL histidine diluent + 2000 mcg vial
- 5 mL histidine diluent + 5000 mcg vial
- 8 mL histidine diluent + 8000 mcg vial

Factor X Human

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Control and Treatment of Bleeding; Hereditary Factor X Deficiency Disease
Initial, 30 international units/kg IV infusion at the first sign of bleeding. Repeat every 24 hours until bleeding stops. **MAX 60 international units/kg/day**.[1].

Perioperative Management of Bleeding; Hereditary Factor X Deficiency Disease, Mild to Moderate
Pre-surgery: To get initial dose, calculate dose to raise factor X levels to between 70 and 90 international units/dL. **MAX 60 international units/kg/day**[1].
Post-surgery: Repeat dose as needed to maintain factor X levels at a minimum of 50 international units/dL until risk of bleeding subsides. **MAX 60 international units/kg /day**[1].

Prophylaxis of Bleeding Episodes; Hereditary Factor X Deficiency Disease
Initial, 40 international units/kg IV infusion twice weekly. Adjust dosage regimen to clinical response and trough levels of Factor X of at least 5 international units/dL. Do not exceed a peak level of 120 international units/dL. **MAX 60 international units/kg/day**[1].

Dose Calculations
Individualize dose according to clinical situation.
Dose (international units) = body weight (kg) times desired factor X increase (international units/dL) times 0.6; **MAX 60 international units/kg/day** IV infusion [1]
Estimate the expected *in vivo* peak increase in factor X level expressed as international unit/dL (or % normal), using following formula:
Estimated increment of factor X (international unit/dL or % of normal) = [total dose (international units)/body weight (kg)] times 1.7[1]

Uses

Pediatric FDA Approved Indications
•Routine prophylaxis to reduce the frequency of bleeding episodes in pediatric patients with hereditary factor X deficiency [1].
•On-demand control and treatment of bleeding episodes in pediatric patients with hereditary factor X deficiency [1].
•Perioperative management of bleeding in pediatric patients with *mild to moderate* hereditary factor X deficiency. Use of factor X human for perioperative management of bleeding with major surgery in patients with *severe* hereditary factor X deficiency has not been studied [1].

Administration

Administer by IV infusion at a rate of 10 mL/min; **MAX rate 20 mL/min**. After dilution, the final concentration is approximately 100 international units/mL [1].

MEDICATION SAFETY

Contraindications/Precautions

Precautions
Allergic hypersensitivity reactions may occur, including anaphylaxis [1].
Factor X human **neutralizing antibodies or inhibitors** may develop [1].
Infectious agent transmission may occur, including a risk of exposure to viruses, Creutzfeldt-Jakob disease or variant Creutzfeldt-Jakob disease, and other pathogens [1].

Adverse Effects

During clinical trials, adverse reactions were reported in 2 out of 18 patients. The reported adverse effects were infusion site erythema (5.6%), fatigue (5.6%), back pain (5.6%), and infusion site pain (5.6%) [1].

Monitoring

•Monitor plasma factor X activity and confirm adequate levels have been achieved and maintained by performing a validated test (eg, one-stage clotting assay) [1].
•For perioperative use, measure post-infusion factor X activity before and after surgery [2].
•For prophylaxis of bleeding episodes, trough blood levels of Factor X should be monitored at intervals, especially in the first weeks of therapy or after dosages changes. [1].
•Monitor for development of neutralizing antibodies (inhibitors). If expected activity levels are not attained or if bleeding is not controlled with an appropriate dose, perform an assay measuring inhibitor concentration (Nijmegen-Bethesda inhibitor assay) [1].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of Action

Factor X is converted from its inactive form to the active form (factor Xa) and with factor Va on the phospholipid surface forms a prothrombinase complex, which activates prothrombin to thrombin in the presence of calcium ions. Thrombin acts upon soluble fibrinogen and factor XIII to generate a cross-linked fibrin clot [2].

Concentrations
The mean $AUC_{0 \text{ to infinity}}$ of factor X was 18 international units x hr/mL and mean factor X Cmax was 0.504 international units/mL in patients with severe or moderate Factor X deficiency following a single IV dose of 25 international units/kg. The pharmacokinetics of factor X is similar following single and repeat dosing [2].

Distribution
The factor X Vd at steady state is 56.3 mL/kg [2].

Total Body Clearance
The clearance of factor X is 1.35 mL/kg/hr [2].

Half-life
The half-life of factor X is 30.3 hours [2].

ABOUT

Special Considerations/Preparation

Supplied as single use vials with 250 or 500 international units packaged with 2.5 or 5 mL of sterile water for injection, respectively. *Each vial is labeled with the actual factor X potency/content in international units* [1].
Refrigerate in original package or store at room temperature between 36 and 86 degrees F. Protect from light and do not freeze [1].

Preparation
Reconstitute with provided diluent (sterile water for injection) and transfer device (Mix2Vial); a suitable needle and syringe will also be necessary (not provided) [1]
Vials and diluent should be brought to room temperature before reconstitution. Final concentration is approximately 100 international units/mL after reconstitution [1]
When reconstituting, the diluent will automatically transfer into the drug vial by the vacuum contained within it. Do not use if the diluent is not pulled into the vial of the drug. Swirl, do not shake the vial [1]
If more than 1 vial is needed, use a new Mix2Vial for each [1]
Final product should be clear to slightly pearl in color. Do not use if discolored or particulate matter is present [1]
Use the product immediately after reconstitution [1]
After reconstitution, administer within 1 hour [1].

Factor XIII Concentrate, Human

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Congenital factor XIII (FXIII) deficiency

Optimal dosage in neonates is unknown; individualize dose based on FXIII activity level and clinical response or if applicable, type of surgery. The following are the recommendations for adults and children.

Initial dose, 40 international units/kg IV every 28 days *for prophylaxis*[1][2]. *For perioperative management,* administer full prophylactic dose if it has been 21 to 28 days since last dose. Administer a partial or full dose (based on FXIII activity level) if it has been 8 to 21 days since last dose. An additional dose may not be needed if it has been 7 days or less since last dose [1].

Dosage adjustment: Children younger than 16 years may require dose adjustments based on a shorter half-life and faster clearance compared with adults [1]. Neonates may have shorter half-lives [3].

Using the Berichrom Activity Assay, increase dose by 5 international units/kg for a FXIII activity trough level of less than 5% or decrease dose by 5 international units/kg for 2 trough levels greater than 20% or one trough level greater than 25%. Maintain dose for trough level of 5% to 20% [1].

Uses

FDA approved indication

Coagulation factor XIII is indicated for prophylaxis and perioperative management of surgical bleeding in pediatric patients with congenital factor XIII deficiency [1].

Administration

Do not exceed 4 mL/min during administration. The final concentration of factor XIII solution is 50 to 80 international units/mL [1].

MEDICATION SAFETY

Contraindications/Precautions

Contraindicated in patients with anaphylactic or severe systemic reaction to human plasma-derived products or to any other component of the product [1].

Precautions
This product is a human plasma derivative and there is an increased risk of transmission of infectious agents, including viruses and theoretical risk of Creutzfeldt-Jakob disease agent [1].
Hypersensitivity reactions have been reported. If anaphylaxis or hypersensitivity reaction occur, immediately discontinue and institute appropriate treatment [1].
Development of inhibitory antibodies have been detected [1].
Thromboembolic complications have been reported [1].

Adverse Effects

The most common adverse reactions are joint inflammation, hypersensitivity, arthralgia, rash, pruritus, erythema, hematoma, headache, elevated thrombin-antithrombin levels, and increased blood lactate dehydrogenase [1].

Monitoring

Monitor trough Factor XIII activity levels during treatment, and during and after surgery, to maintain an activity level of 5% to 20% [1].
Monitor for development of inhibitory antibodies. If an adequate response is not seen with appropriate doses or bleeding is not controlled, perform an assay that measures factor XIII inhibitory antibody concentrations [1].
Monitor for thromboembolic complications in patients with known risk factors [1].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Coagulation Factor XIII Concentrate (Human) is a heat-treated lyophilized concentrate made from pooled human plasma. Coagulation Factor XIII Concentrate is an endogenous plasma glycoprotein made up of both A and B subunits. Factor XIIIa promotes cross-linking of fibrin during coagulation and is essential to protecting against fibrinolysis. Cross-linked fibrin provides tensile strength to a primary hemostatic platelet plug [1].

Compared with adults, patients younger than 16 years had a shorter half-life (5.7 days vs 7.1 days) and faster clearance (0.29 mL/hr/kg vs 0.22 mL/hr/kg) [1].

ABOUT

Special Considerations/Preparation

Available as lyophilized powder in single use vials containing 1000 to 1600 international units. Each vial label and carton states the actual units of potency of factor XIII [1].
Prior to reconstitution, store between 2 and 8 degrees C (36 and 46 degrees F); protect from light. Do not freeze [1].
Factor XIII may be stored at 25 degrees C (77 degrees F) for up to 6 months. Do not return to refrigerator after it is stored at room temperature [1].

Preparation:
Allow Factor XIII and diluent to reach room temperature. Reconstitute factor XIII concentrate (human) with 20 mL sterile water for injection for a final concentration of 50 to 80 international units/mL. Do not shake vial [4].
The solution must be used within 4 hours after reconstitution. Do not refrigerate or freeze the reconstituted solution [4].
Once reconstituted, the solution should be at room temperature upon administration [4].

Famotidine

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

IV: 0.25 to 0.5 mg/kg/dose IV every 24 hours.
Continuous infusion of the daily dose in adults provides better gastric acid suppression than intermittent dosing.
Oral: 0.5 to 1 mg/kg/dose orally every 24 hours.

Uses

Prevention and treatment of stress ulcers and GI hemorrhage aggravated by gastric acid secretion.
Apnea of prematurity: Reducing gastric acidity or increasing gastric motility for the sole purpose to reduce apnea episodes is not supported by the literature [3].
Crying and irritability: In otherwise healthy term infants, histamine$_2$ receptor antagonists or proton pump inhibitors should not be used for the treatment of crying and distress [4].
Gastroesophageal Reflux (GER): The risks associated with acid reducing agents outweighs the benefits in preterm infants for GER. Acid blocking agents should not be used and if used in preterm infants, use sparingly [5]. In otherwise healthy term infants, histamine$_2$ receptor antagonists or proton pump inhibitors should not be used for the treatment of visible regurgitation [4].
Gastroesophageal Reflux Disease (GERD): Proton pump inhibitors (PPIs) are the first-line agents for erosive esophagitis in infants and children with GERD. Histamine$_2$ receptor antagonists are the second-line agent if PPIs are not available or are contraindicated. A duration of treatment for 4 to 8 weeks for GERD symptoms is recommended. Regularly reassess the need for long-term acid suppression. If no response after 4 to 8 weeks, then re-evaluate for other causes of symptoms. H_2RAs and PPIs are not recommended for extraesophageal symptoms (e.g. cough, wheezing, asthma), unless GERD symptoms are present and/or GERD has been diagnosed [4].
A trial use of PPIs as a diagnostic test for GERD is not recommended in infants or in patients presenting with extraesophageal symptoms. However, in children with typical GERD symptoms, a trial of 4 to 8 weeks with a PPI may be used as a diagnostic test [4].

Pediatric FDA Approved Indications
Intravenous:
Treatment of pathological hypersecretory conditions or intractable duodenal and gastric ulcers, or as an alternative to the oral dosage form for short-term use in patients who are unable to take oral medication [6].

Oral

Suspension is indicated for [2]:

- Short-term treatment of patients with symptoms of gastroesophageal reflux disease (GERD)
- Short-term treatment of esophagitis due to GERD including erosive or ulcerative disease diagnosed by endoscopy
- Peptic ulcer in pediatric patients 1 year or older

Administration

IV Intermittent: Dilute to concentration of 2 to 4 mg/mL with 0.9% NS; give over a period of at least 2 minutes. Alternatively, dilute to concentration of 0.2 mg/mL with D_5W or other compatible solution and infuse over 15 to 30 minutes [1].
Oral: Shake oral suspension vigorously for 5 to 10 seconds prior to each use; unused constituted oral suspension should be discarded after 30 days [2].

MEDICATION SAFETY

Contraindications/Precautions

PRECAUTIONS
Gastrointestinal: Symptomatic response does not rule out gastric malignancy [2]
Infection: Increased risk of infections (necrotizing enterocolitis, pneumonia, upper respiratory tract infections, sepsis, urinary tract infections, and *Clostridium difficile* infections) in infants and children on H_2 blockers or PPIs demonstrated in case-control studies [4][7].
Renal: CNS adverse effects have been reported in patients with moderate and severe renal insufficiency; dosage adjustment recommended [2]

Adverse Effects

The use of H2 blockers in preterm infants has been associated with an increased risk for late-onset bacterial and fungal sepsis. Routine gastric acid suppression in neonates should be avoided. No short term adverse effects have been reported in infants and children, although data are limited to a few small studies. The most common (less than 5% of patients) adverse effects noted in adults were headache, dizziness, constipation, and diarrhea.

The use of H2-blockers in preterm infants has been associated with facilitating *Candida* species colonization [8], and an increased risk for late-onset bacterial and fungal sepsis [9][8].
In a prospective, multicenter, observational study comparing VLBW neonates receiving raNITIdine (n=91) to those not receiving raNITIdine (n=183), neonates receiving raNITIdine

had an increased rate of infection (37.4% versus 9.8%; OR 5.5; 95% CI, 2.9 to 10.4), increased risk for NEC (9.8% versus 1.6%; OR 6.6; 95% CI, 1.7 to 25), and increased mortality (9.9% versus 1.6%) [10].
In a retrospective, case-control study, H2-blocker use in VLBW infants was associated with an increased incidence of NEC (OR 1.7; 95% CI, 1.34 to 2.19) [11].

Solution Compatibility

D_5W, $D_{10}W$, and NS

Terminal Injection Site Compatibility

Acyclovir, aminophylline, amiodarone, ampicillin, atropine, aztreonam, calcium gluconate, caspofungin, cefazolin, cefotaxime, cefoxitin, ceftazidime, ceftriaxone, dexamethasone, digoxin, dobutamine, dopamine, enalaprilat, epinephrine, erythromycin lactobionate, esmolol, fluconazole, flumazenil, furosemide, gentamicin, heparin, hydrocortisone succinate, imipenem/cilastatin, insulin, isoproterenol, lidocaine, linezolid, lorazepam, magnesium sulfate, metoclopramide, mezlocillin, midazolam, morphine, nafcillin, nicardipine, nitroglycerin, oxacillin, phenytoin, piperacillin, potassium chloride, procainamide, propofol, remifentanil, sodium bicarbonate, sodium nitroprusside, ticarcillin/clavulanate, vancomycin, and vitamin K_1.

Terminal Injection Site Incompatibility

Azithromycin, cefepime and piperacillin/tazobactam.

Monitoring

Gastric pH may be measured to assess efficacy (greater than 4).

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action: Inhibits gastric acid secretion by histamine H_2-receptor antagonism.

Elimination half-life is dependent on renal function, and decreases with age from 11 hours (range 5 to 22) in neonates to 8 hours (range 4 to 12) by 3 months of age. Oral bioavailability is 42 to 50%.

ABOUT

Special Considerations/Preparation

Availability

Injection: 0.4 mg/mL and 10 mg/mL.

10-mg/mL solution for intravenous use in 2-mL preservative-free single-dose vials, and 4-mL multidose vials containing 0.9% (9 mg/mL) benzyl alcohol as a preservative. A 1-mg/mL dilution may be made by adding 1 mL of the 10 mg/mL concentrated solution to 9 mL of sterile water for injection. Dilution stable for 7 days at room temperature. Although diluted Pepcid® Injection has been shown to be physically and chemically stable for 7 days at room temperature, there are no data on the maintenance of sterility after dilution. Therefore, it is recommended that if not used immediately after preparation, diluted solutions of Pepcid® Injection should be refrigerated and used within 48 hours [6][12].

Oral: 10-mg, 20-mg, and 40-mg tablets; 40 mg/5 mL (8 mg/mL) oral powder for suspension.

Pepcid® for oral suspension is supplied as a powder containing 400 mg famotidine. Constitute by slowly adding 46 mL Purified Water and shaking vigorously for 5-10 seconds. Final concentration 40 mg/5 mL (8 mg/mL). Stable at room temperature for 30 days. Shake bottle before each use.

Extemporaneous Oral Suspension

Famotidine 8 mg/mL oral suspension was stable in amber polyethylene tetraphthalate bottles for 95 days at 23 to 25°C[13]:

- Triturate seventy 40-mg tablets of famotidine into a paste with sterile water for irrigation
- Dilute with equal volumes of Ora-Plus and Ora-Sweet to a final volume of 350 mL
- Blend until uniform
- Shake well before use

Fat Emulsion

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Critical Dosing Notes:
• Clinolipid®: Prior to administration, correct severe water and electrolyte disorders, severe fluid overload states, and severe metabolic disorders. Baseline serum triglycerides should be established prior to starting the infusion. In patients with elevated triglyceride levels, initiate at a lower dose and check triglyceride levels prior to advancing in smaller increments [1].
• Intralipid®: Prior to administration, correct severe fluid and electrolyte disorders and measure serum triglyceride levels to establish a baseline value. In patients with elevated triglyceride levels, initiate at a lower dosage and titrate in smaller increments [2].
• Nutrilipid®: Prior to initiation, determine serum triglyceride levels and correct severe fluid and electrolyte disorders, severe fluid overload states, and severe metabolic disorders [3].
• Omegaven®: Prior to initiation, determine serum triglyceride levels and correct severe fluid and electrolyte disorders [4].
• Infusion rate: Infusion rates may vary between different products. Studies in preterm neonates reported infusion rates between 0.125 to 0.17 g fat/kg/hour [5][6]. Rates of 0.2 g fat/kg/hour or less have been suggested for this population [7].

Clinolipid®
Total Parenteral Nutrition and Essential Fatty Acid Deficiency (treatment and prophylaxis)
Birth (including preterm and term neonates) to 2 years: Initial, 0.5 g/kg/day IV, increasing based on infant's ability to eliminate fat; **MAX dose 3 g/kg/day or 60% of total energy requirements**[1].
Infusion rate: 0.1 to 0.2 mL/kg/hour for the first 15 to 30 minutes; gradually increase to required rate after 30 minutes. **MAX infusion rate, 0.75 mL/kg/hour**[1].

Intralipid® 20%
Total Parenteral Nutrition and Essential Fatty Acid Deficiency (treatment and prophylaxis)
Birth (including preterm and term neonates) to 2 years: Initial, 0.5 g/kg/day IV, increasing based on infant's ability to eliminate fat, up to a **maximum dosage of 3 g/kg/day or 60% of total energy requirements**[2].
Infusion rate: 0.1 mL/kg/hour for the first 10 to 15 minutes; gradually increase to required rate after 15 minutes. **MAX infusion rate, 0.75 mL/kg/hour**[2].

Intralipid® 30%
Total Parenteral Nutrition and Essential Fatty Acid Deficiency (treatment and prophylaxis)
Premature infants: Initial, 0.5 g/kg/day IV; may be increased in relation to the infant's ability to eliminate fat; **MAX dose, 3 g/kg/day or 60% of total energy requirements**[8]
Premature infants, Infusion rate: MAX rate, 0.5 mL/kg/hour[8]

Older pediatric patients: MAX dose, 3 g/kg/day or 60% of total energy requirements[8]
Older pediatric patients, Infusion rate: Initial, 0.01 g fat/minute IV for first 10 to 15 minutes, then increase to 0.1 g fat/kg/hour; **MAX rate 0.5 mL/kg/hour**[8]

Nutrilipid® 20%
Total Parenteral Nutrition and Essential Fatty Acid Deficiency (treatment and prophylaxis)
Birth (including preterm and term neonates) to younger than 1 year Initial, 1 to 2 g/kg/day IV over 12 to 24 hours; **MAX dose, 3 g/kg/day or 60% of total energy requirements**[3].
Infusion rate: 0.05 mL/kg/hour for the first 10 to 15 minutes; gradually increase to required rate after 15 minutes. **MAX infusion rate, 0.75 mL/kg/hour**[3].

Omegaven® 10%
Total parenteral nutrition-associated cholestasis (treatment only)
Initiate therapy as soon as direct or conjugated bilirubin levels are 2 mg/dL or greater in pediatric patients who are expected to be parenteral nutrition-dependent for at least 2 weeks [9].
Dosage: 1 g/kg/day IV administered over 8 to 24 hours depending on clinical situation; **MAX dose, 1 g/kg/day** [9].
Infusion rate: 0.2 mL/kg/hour for the first 15 to 30 minutes, then gradually increase to the required rate after 30 minutes. **MAX infusion rate, 1.5 mL/kg/hour**[9].
Duration: Continue therapy until direct bilirubin levels are less than 2 mg/dL or until the patient no longer requires parenteral nutrition [9].

Smoflipid® 20%
Total Parenteral Nutrition
Birth (including preterm and term neonates) to 2 years: Initial, 0.5 to 1 g/kg/day; **MAX dose, 3 g/kg/day or 60% of total energy requirements**
Infusion rate: 0.1 to 0.2 mL/kg/hour for the first 15 to 30 minutes, then gradually increase to the required rate after 30 minutes. **MAX infusion rate, 0.75 mL/kg/hour**[10]

Dose Adjustments
Renal impairment: No specific recommendations are available [8][3][2][10][9]
Hepatic impairment: No specific recommendations are available [8][2][3][10][9]
Fat overload syndrome: Stop infusion [3][2][10]
Hypersensitivity reaction: Stop infusion immediately and initiate appropriate supportive measures [3][2][10][9]
Elevated triglyceride levels, Intralipid® or Nutralipid®: In patients with elevated triglyceride levels, initiate at a lower dose and advance in smaller increments [1][3][2]
Hypertriglyceridemia, Omegaven® (serum triglycerides greater than 250 mg/dL in neonates or infants or greater than 400 mg/dL in older children): Consider discontinuing for 4 hours; resume as indicated based on repeat serum triglyceride level. If triglycerides remain elevated, consider a dose reduction of 0.5 to 0.75 g/kg/day with an incremental increase to 1 g/kg/day [4].
Parenteral nutrition-associated liver disease (PNALD): Consider discontinuation or dosage adjustment if liver test abnormalities occur [3][2][10]
Poor clearance of lipids from circulation: Stop the infusion and initiate medical evaluation [8][3][2][10][9]

Uses

Place in Therapy: Multicomponent fish oil-containing lipid emulsions are recommended when long-term use of parenteral nutrition in children is anticipated. The optimal strategy (lipid reduction or source of lipid) for IV lipids in neonates and older children to prevent or treat liver complications is unknown. Long-term effects on fatty acid profile, growth, and neurodevelopment in children are unknown [16].

Omegaven

In 2 prospective open-label trials in 80 pediatric patients (3 to 42 weeks of age, including preterm neonates with estimated gestational age of more than 24 weeks at birth) with parenteral nutrition-associated cholestasis (PNAC), administration of fish oil triglyceride emulsion as part of a parenteral nutrition regimen was associated with a median decrease in direct bilirubin level from 3.8 mg/dL at baseline to 0.6 mg/dL (interquartile range, 0.1 to 2.8 mg/dL). Historical control patients (n=41) who received a soybean oil-based lipid emulsion had similar age-appropriate growth; 63% of those receiving fish oil triglycerides and 59% of control patients achieved full enteral feeding by the end of the study [11].

Combination lipid emulsions vs Standard lipid emulsions

Combination lipid emulsions compared with standard lipid emulsions (soybean oil) were safe and well tolerated in 2 meta-analysis of infants younger than 12 months and neonates including preterm neonates [17][18]. Different lipid emulsion formulations during short-term use did not change the rate of cholestasis (6 studies) or elevated bilirubin concentrations (5 studies) in preterm infants, neonates, and children in a meta-analysis [16]. Another meta-analysis had similar findings [18]. Prolonged parenteral fish oil-containing lipid emulsions in children with intestinal failure may decrease bilirubin concentrations [16][19]. The mean changes in total bilirubin concentration from baseline to day 29 were significantly different between Smoflipid (-1.5 mcmol/L) and Intralipid (+2.3 mcmol/L) in a randomized, double-blind study of 28 children (mean age 30.3 and 38.8 months, respectively) with short bowl syndrome, chronic intestinal pseudo-obstruction, or congenital disease of intestinal mucosa. Plasma α-tocopherol and ω-3 fatty acid (eicosapentaenoic acid and docosahexaenoic acid) increased significantly more with Smoflipid. Lipid peroxidation indices were not different between the 2 groups [19]. No statistically significant differences in parenteral nutrition-associated liver disease and other clinical outcomes (death, growth, lung disease, infection, necrotizing enterocolitis (stage 2 or more), intraventricular hemorrhage (grade III to IV), difference in patent ductus arteriosus, or severe eye disease (retinopathy of prematurity stage 3 or more) in preterm neonates were demonstrated between Smoflipid and standard lipid emulsion in a meta-analysis of 7 studies (n=469) [17].

Pediatric FDA Approved Indications

Clinolipid®

Clinolipid is indicated in pediatric patients, including term and preterm neonates, as a source of calories and essential fatty acids for parenteral nutrition (PN) when oral or enteral nutrition is not possible, insufficient, or contraindicated [1].

Intralipid® and Nutrilipid®
• Intralipid® 20% and Nutrilipid® 20% fat emulsions are indicated as a source of calories and essential fatty acids for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated [13][12]
• Intralipid® 30% fat emulsion is indicated for the preparation of 3-in-1 or total nutrient admixtures as a source of calories and essential fatty acids in adult and pediatric patients requiring parenteral nutrition for an extended time (usually more than 5 days) [15]

Smoflipid®
• Smoflipid® (fat emulsion/fish oil/soybean oil) injectable lipid emulsion is indicated in pediatric patients, including term and preterm neonates, as a source of calories and essential fatty acids for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated [14]

Omegaven®
• Omegaven® is indicated as a source of calories and fatty acids in pediatric patients with parenteral nutrition-associated cholestasis (PNAC) [4]
• Omegaven® is not indicated for the prevention of PNAC. It has not been demonstrated that Omegaven(R) prevents PNAC in parenteral nutrition (PN)-dependent patients [4]
• It has not been demonstrated that the clinical outcomes observed in patients treated with Omegaven(R) are a result of the omega-6:omega-3 fatty acid ratio of the product [4]

Administration

General Information
• For IV infusion through a central or peripheral line only [1][11][12][13][14].
• **Intralipid® 30%:** Not for direct infusion; it must be infused as part of an admixture into a central or peripheral vein [15]
• **Pharmacy bulk package (1000 mL container):** For admixing use only and not intended for direct IV administration [1][13][12].

Specific Administration Information
• Use a 1.2 micron in-line filter [1][14][13][12][15][4].
• Do not administer through di-2-ethylhexyl phthalate (DEHP) sets or lines [1][14][15][13][12][4].
• Can be infused concurrently into same vein as dextrose-amino acid solutions (as part of parenteral nutrition) by a Y-connector located near the infusion site; flow rates should be controlled separately by individual pumps [14][13][12][4].
• When administered with amino acids and dextrose, the choice of central vs peripheral route will depend on osmolarity of the final infusate [1][14][4][13]. Admixtures greater than or equal to 900 mOsm/L osmolarity must be infused through a central vein; osmolarity less than 900 mOsm/L may be administered peripherally [14][4].
• To prevent air embolism use a nonvented infusion set or close the vent on a vented set, avoid multiple connections, do not connect flexible bags in series, fully evacuate residual gas in the bag prior to administration, do not pressurize the flexible bag to increase flow rates [1][14][13][12]. For Omegaven®, use a vented infusion set when infused from the bottle [4].

• If using Nutrilipid® 20% bags for direct infusion, do not use or penetrate the blocked port [3].

MEDICATION SAFETY

Contraindications/Precautions

Contraindications

Clinolipid

• Known hypersensitivity to egg, soybean, peanut or to any of the ingredients, including excipients [1]

• Severe disorders of lipid metabolism characterized by hypertriglyceridemia (serum triglyceride greater than 1000 mg/dL) [1]

Intralipid®

• Known hypersensitivity to egg, soybean, peanut or to any of the ingredients, including excipients [12]

• Severe disorders of lipid metabolism characterized by hypertriglyceridemia (serum triglyceride greater than 1000 mg/dL) [12]

• Disturbances of normal fat metabolism such as pathologic hyperlipemia, lipoid nephrosis, or acute pancreatitis if accompanied by hyperlipidemia [8]

Nutrilipid®

• Known hypersensitivity to egg, soybean, peanut or to any of the ingredients, including excipients [3]

• Severe disorders of lipid metabolism characterized by hypertriglyceridemia (serum triglyceride greater than 1000 mg/dL) [3]

Omegaven®

• Hypersensitivity to fish or egg protein or to any of the active ingredients or excipients [4].

• Severe hemorrhagic disorders [4]

• Severe disorders of lipid metabolism characterized by hypertriglyceridemia (serum triglyceride concentrations greater than 1000 mg/dL) [4].

Smoflipid®

• Known hypersensitivity to fish, egg, soybean, peanut, or to any ingredient of the product [10].

• Severe disorders of lipid metabolism characterized by hypertriglyceridemia (serum triglyceride concentrations greater than 1000 mg/dL) [14].

Precautions

Endocrine and metabolic: Fat overload syndrome has been reported with IV lipid formulations; increased risk when lipid doses are exceeded, but also reported when administered as recommended. May be reversible upon discontinuation [14]

Endocrine and metabolic: Metabolic acidosis has been reported in neonates and infants after rapid infusion of IV lipid emulsions; preterm and small-for-gestational-age infants may be at an increased risk. Adhere to the recommended total daily dosages and hourly infusion rate; monitoring required and dosage interruption and supportive therapy may be necessary [10]

Endocrine and metabolic: Refeeding Syndrome may occur in severely undernourished patients with parenteral nutrition; thiamine deficiency and fluid retention may also develop.

Carefully monitor severely undernourished patients and slowly increase their nutrient intakes and avoid overfeeding [14].
Endocrine and metabolic: Hypertriglyceridemia has been reported with in increased risk in patients with inherited lipid disorders, obesity, diabetes mellitus, metabolic syndromes and with excessive dextrose administration, monitoring recommended and therapy interruption may be necessary [14].
Endocrine and metabolic: Worsening of preexisting hypertriglyceridemia may occur; monitoring recommended and therapy interruption may be necessary [14]
Endocrine and metabolic: Essential fatty acid deficiency has been reported; monitoring recommended [14]
Hematologic: Use caution in patients with anemia or blood coagulation disorders [20].
Hematologic: Use caution in patients at risk of fat embolism [20].
Hepatic: Parental Nutrition Associated Liver Disease has been reported and can present as cholestasis or steatohepatitis; monitoring recommended and consider discontinuation or dose reduction if abnormalities occur [14].
Hepatic: Parental nutrition-associated cholestasis has been reported in neonates and infants; monitoring recommended and consider discontinuation or dose adjustments if abnormalities occur [10].
Hepatic: Hepatobiliary disorders, including cholecystitis and cholelithiasis, have been reported in patients without preexisting liver disease; monitoring recommended [14].
Hepatic: Use caution in patients with severe liver damage [20].
Immunologic: Hypersensitivity reactions may occur; if suspected, stop infusion and initiate appropriate treatment and supportive measures [14].
Immunologic: Infection may occur as a result of the use of catheters; monitoring recommended including frequent checks of the parenteral access device [14].
Renal: The aluminum contained in the emulsion may reach toxic levels with prolonged administration in patients with impaired kidney function; preterm infants are at greater risk. Patients with impaired kidney function who receive parenteral levels of aluminum at greater than 4 to 5 mcg/kg/day accumulate aluminum at levels associated with central nervous system and bone toxicity; tissue loading may occur at even lower rates of administration [14].
Respiratory: Acute respiratory distress has been reported in neonates and infants after rapid infusion of IV lipid emulsions; preterm and small-for-gestational-age infants may be at an increased risk. Adhere to the recommended total daily dosages and hourly infusion rate; monitoring required and dosage interruption and supportive therapy may be necessary [10]
Respiratory: Use caution in patients with pulmonary disease [20].
Special populations: Clinical decompensation and/or death have been reported in neonates and infants after rapid infusion of IV lipid emulsions; preterm and small-for-gestational-age infants may be at an increased risk. Adhere to the recommended total daily dosages and hourly infusion rate; monitoring required and dosage interruption and supportive therapy may be necessary [10]

Adverse Effects

Clinolipid®
Adverse reactions that occurred in ≥ 5% of patients included hyperbilirubinemia, patent ductus arteriosus, anemia, gastroesophageal reflux disease, bradycardia, feeding intolerance,

neonatal intraventricular hemorrhage, increased alkaline phosphatase, atrial septal defect, hyponatremia, sepsis, and infantile apnea [1]

Intralipid
Adverse effects that occur more frequently with Intralipid-treated patients includes contamination of the IV catheter resulting in sepsis and vein irritation by concurrently infused hypertonic solutions which may result in thrombophlebitis. These adverse effects are inseparable from the hyperalimentation procedure with or without Intralipid [20]

Nutrilipid
The most commonly reported adverse effects were hyperlipidemia, hypercoagulability, thrombophlebitis, and thrombocytopenia. Additional adverse effects reported in long-term use include hepatomegaly, jaundice, splenomegaly, thrombocytopenia, leukopenia, liver function test abnormalities, brown pigmentation of the liver, and overloading syndrome [13].

Omegaven
The most common adverse reaction with Omegaven-treated pediatric patients were vomiting (46%), agitation (35%), bradycardia (35%), apnea (20%), viral infection (16%), and erythema (12%) [11].

Smoflipid
There was no difference in the incidence of infection between combination lipid emulsions (Smoflipid or Lipoplus) and standard lipid emulsions (soybean oil only) in a meta-analysis (6 trials) of neonates and infants younger than 12 months [18].

There were no differences observed between Smoflipid and Intralipid in acid-base status, platelet counts, and biochemical parameters (including triglycerides, bilirubin (total and direct), and alanine aminotransferase on postnatal days 2, 4, and 7 in a randomized trial of 96 very low birth infants. The potassium and aspartate aminotransferase concentrations were significantly higher, but within normal limits for preterm infants, in the Smoflipid group [21]. There was no difference in the elevation of triglycerides in preterm neonates (n=60) between Smoflipid for a mean duration of 11 days and Intralipid for a mean duration of 10 days [6]. The association between cholestasis and different lipid concentrations has not been established [16].

Monitoring

Toxic Laboratory Monitoring
• Carefully monitor pediatric patient's ability to eliminate the infused lipids from the circulation (eg, measure serum triglycerides, plasma free fatty acid levels, or both) [9].
• Obtain serum triglyceride levels before starting the infusion and regularly during therapy [4]. Additionally, check serum triglyceride levels before each dosage adjustment in patients with elevated triglyceride levels [1].
• Carefully assess lab test results (eg, leukocytosis, hyperglycemia) for signs of early infection [4].
• Monitor for signs and symptoms of fat overload (eg, anemia, leukopenia, thrombocytopenia, coagulation disorders, hyperlipidemia, and deteriorating liver function) [4]

• Carefully monitor severely malnourished patients for signs of refeeding syndrome (eg, intercellular shifts of potassium, phosphorus, and magnesium, and thiamine deficiency) [4].
• Monitor fluid and electrolyte status, serum osmolarity, blood glucose, liver and kidney function, coagulation parameters, and complete blood count, including platelets, throughout treatment [9], with frequent monitoring of platelet counts in neonates [20]
• Perform liver function tests to monitor for parenteral nutrition-associated liver disease and other hepatobiliary disorders [20].
• Monitor for laboratory evidence of essential fatty acid deficiency; laboratory tests are available to determine serum fatty acid levels; reference values should be consulted to help determine adequacy of essential fatty acid status [4].
• Monitor fluid status closely in patients with pulmonary edema or heart failure [9].
Laboratory interference: Omegaven® may interfere with some laboratory blood tests (e.g., hemoglobin, lactate dehydrogenase, bilirubin, and oxygen saturation) if blood is sampled before lipids have cleared from the bloodstream. Perform these tests at least 6 hours after the lipid infusion is stopped [9]

Toxic Physical Monitoring
• Monitor for signs or symptoms of hypersensitivity reactions [4].
• Carefully monitor patients for signs and symptoms of early infection (eg, fever, chills) and frequently inspect the parenteral catheter insertion site [4].
• Carefully monitor severely malnourished patients for symptoms of refeeding syndrome (eg, fluid retention) [4].
• Monitor for signs and symptoms of fat overload (eg fever, hepatomegaly, and CNS manifestations [eg, coma]) [4]
• Monitor patients for signs and symptoms of essential fatty acid deficiency (eg, fluid retention) [4].
• Monitor fluid status throughout treatment and especially in patients with pulmonary edema or heart failure [1].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action: Intravenous fat emulsions provide a source of calories and essential fatty acids. Beta oxidation of fatty acids provide energy. Fatty acids are necessary for membrane structure and function, precursors for bioactive molecules (e.g. prostaglandins), and as regulators of gene expression [22][13].

Pharmacokinetics: Infused fat particles cause a transient increase in plasma triglyceride concentrations. The triglycerides are then hydrolyzed to free fatty acids and glycerol by lipoprotein lipase. The free fatty acids either enter the tissues (to be oxidized or resynthesized to triglycerides for storage) or circulate, bound to albumin in the plasma, and subsequently may undergo hepatic oxidation or conversion to very low–density lipoproteins (VLDL) that re-enter the bloodstream. Fat emulsions also contain phosphatides and glycerol. Phosphatides are involved in the formation of membrane structures; choline (a component of phosphatides) prevents deposition of fat in the liver; and glycerol is metabolized to carbon dioxide and glycogen or is used in the synthesis of fats [13].

ABOUT

Special Considerations/Preparation

Comparison of Fat Emulsions

[11][23][24][25][12][13]

	Fat Emulsion				
	Clinolipid®	**Intralipid® 20%**	**Nutrilipid® 20%**	**Omegaven 10% ***	**Smoflipid® 20%**
Oils (%)					
Soybean	4	20	20	0	6
Olive	16	0	0	0	5
Fish	0	0	0	10	3
Coconut palm or oil palm (Medium-chain triglycerides)	0	0	0	0	6
Fatty Acid Content (%)					
Linoleic	13.8 to 22	44 to 62	48 to 58	1.5	14 to 25
Oleic	44.3 to 79.5	19 to 30	17 to 30	4 to 11	23 to 35
Caprylic	0	0	0	0	13 to 24
Palmitic	7.6 to 19.3	7 to 14	9 to 13	4 to 12	7 to 12
Capric	0	0	0	0	5 to 15
Linolenic	0.5 to 4.2	4 to 11	4 to 11	1.1	1.5 to 3.5
Stearic	0.7 to 5	1.4 to 5.5	2.5 to 5	0	1.5 to 4
Eicosapentaenoic	0	0	0	13 to 26	1 to 3.5
Docosahexaenoic	0	0	0	14 to 27	1 to 3.5
Palmitoleic	0 to 3.2	0	0	4 to 10	0
Myristic	0	0	0	2 to 7	0
Arachidonic acid	0	0	0	0.2 to 2	0
Egg yolk phospholipid (%)	1.2	1.2	1.2	1.2	1.2
Glycerin (%)	2.25	2.25	2.5	2.5	2.5
all-rac-α-tocopherol (mg/mL)	0	0	0	0.15 to 0.3	0.163 to 0.225
Calories (Kcal/mL)	2	2	2	1.12	2
Osmolarity (mOsm/L)	260	260	not provided	273	270

Product Information: Omegaven 7/2018; Smoflipid, Fresenius Kabi 5/2016; Patten, 2016; IntraLipid, Baxter 4/2015; Nutrilipid, Braun 8/2014; Clinolipid, Baxter, 4/2024
KEY: * = Total omega-3 fatty acid content is 40% to 54%

Availability

Clinolipid® 20% is available in 100-, 250-, and 500-mL fill sizes. Clinolipid 20% is also available in a 1000-mL bulk package [1]

Intralipid ® 20% is available in 100-, 250-, and 500-mL fill sizes. Intralipid® 20% is also available in a 1000-mL bulk package [12]and Intralipid® 30% is available in a 500-mL bulk package [20].

Nutrilipid® 20% is supplied as a sterile emulsion in 250- or 500-mL volumes. Also available as a pharmacy bulk package (1000 mL) not intended for direct IV administration [13].

Omegaven ® 10% is available as 5 g/50 mL and 10 g/100 mL [11].

Smoflipid ® 20% is available as a sterile lipid injectable emulsion in 100-, 250-, and 500-mL sizes. Also available as a 1000-mL Pharmacy Bulk Package [26]

Storage Prior to Admixture

Clinolipid®: Store in overpouch at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F). Protect from freezing and avoid excessive heat. Use immediately upon removal from overpouch. If not used immediately, store at 25 degrees C (77 degrees F) for up to 24 hours. *Pharmacy bulk package* that is not used immediately should be stored for no longer than 24 hours at not more than 25 degrees C (77 degrees F). Once the closure is penetrated use contents within 4 hours [1].

Intralipid®: Store at room temperature below 25 degrees C (77 degrees F). Do not freeze. If not admixed promptly, pharmacy bulk package vial may be stored at a temperature below 25 degrees C (77 degrees F) for a maximum of 4 hours after initial entry [12][20].

Nutrilipid®: Store at a temperature below 25 degrees C (77 degrees F). Do not freeze [13].

Omegaven ®: Store at room temperature below 25 degrees C (77 degrees F); avoid excessive heat. Do not freeze [4].

Smoflipid®: Store in overpouch below 25 degrees C (77 degrees F). Avoid excessive heat. Do not freeze and discard if accidentally frozen. Use immediately upon removal of overpouch. If not used immediately, do not store for more than 24 hours at 2 to 8 degrees C (36 to 46 degrees F). Inspect the integrity indicator prior to removing overpouch; discard if indicator is black. *Pharmacy bulk package* that is not used immediately should be stored under refrigeration between 2 and 8 degrees C (36 and 46 degrees F) for up to 24 hours. After removal from storage and once closure is penetrated use contents within 4 hours [26].

General Preparation Information

- Nutrilipid® 20% bags for direct infusion: Do not use or penetrate the blocked port [3].
- Intralipid® 30%: Combined with total parenteral nutrition fluids; final concentration is not to exceed 20% fat [15].

Preparation/Admixture

- Do not add additives directly [1][15][12][13][14].
- Do not add to the parenteral nutrition container first; destabilization of the lipid may occur [1][15][12][13][14][4].
- May be mixed with amino acid and dextrose solutions with demonstrated compatibility.

Inspect the mixture closely for formation of precipitates [1][15][12][13][14][4].
• The following mixing sequence is necessary to minimize pH-related issues: 1) transfer dextrose to the parenteral nutrition container, 2) transfer amino acid, and 3) transfer lipids. Simultaneous transfer of amino acid, dextrose and lipids using an automated compounding device is also permitted [1][15][12][13][14][4].
• Nutrilipid® 20%: If using an automated device for mixing, Nutrilipid® 20% must be separated from the dextrose product by an amino acid product or other non-acidic products [27].
• Use gentle agitation during admixing to minimize localized concentration effects; shake gently after each addition [1][15][12][13][14][4].
• Visually inspect to assure precipitates have not formed during mixing or addition of additives, and that separation of the emulsion has not occurred (noted by discoloration, phase separation, or oily droplets); discard the admixture if there appears to be separation [1][15][12][13][14][4], or any signs of discoloration, particulates, or leakage are observed [1]..
• Protect the admixed parenteral nutrition solution from light [1][15][12][13][4][14].

Storage and Stability After Admixture
Clinolipid®: If not used immediately, admixtures should be stored for no longer than 24 hours at no more than 25 degrees C (77 degrees F). Once the closure is penetrated use contents within 4 hours [1]
• Infuse admixed parenteral nutrition immediately. If not used immediately store admixture under refrigeration at 2 to 8 degrees C (36 to 46 degrees F) or no longer than 24 hours. Infusion must be complete within 24 hours after removal from refrigeration [15][12] [13][10][4]; discard remaining contents of a partly used bag [4][13].
Omegaven®: If not used immediately, admixtures may be stores for up to 6 hours at room temperature or up to 24 hours under refrigeration; complete the infusion within 24 hours after removal from storage [4].

DOSING/ADMINISTRATION

Dose

Naloxone should be readily available to reverse adverse effects.
Analgesia
Single or intermittent dose: 0.5 to 3 mcg/kg per dose slow IV push [1][2]. Repeat as required (usually every 2 to 4 hours).
Continuous infusion: 0.5 to 2 mcg/kg/hr [1][2]. Tolerance may develop rapidly following constant infusion.

Anesthesia: 5 to 50 mcg/kg IV per dose.

Sedation
Single or intermittent dose: 0.5 to 4 mcg/kg IV per dose. Repeat as required (usually every 2 to 4 hours).
Continuous infusion: 1 to 5 mcg/kg/hr IV. Tolerance may develop rapidly following constant infusion.

Uses

Analgesia: A consensus of the International Evidence-Based Group for Neonatal Pain recommends the use of IV fentaNYL in newborns, using intermittent doses of 0.5 to 3 mcg/kg or a continuous infusion of 0.5 to 2 mcg/kg/hour [2]. Investigators of one clinical trial in preterm neonates (32 weeks or younger) suggested bolus doses only when ventilation will be of short duration and before major painful procedures and to reserve continuous infusions when ventilation is expected to be of longer duration [1].
A continuous infusion of fentaNYL 1 mcg/kg/hr, plus bolus doses of 1 mcg/kg prior to painful procedures, or as needed for severe pain, reduced the incidence of severe, acute procedural pain and severe prolonged pain compared with intermittent 1 mcg/kg bolus doses alone in a randomized, double-blind, placebo-controlled study of use initiated within 72 hours of birth in preterm newborns on mechanical ventilation (n=131; gestational age 22 to 32 weeks). However, no clinically significant difference was demonstrated for prolonged pain. Side effects, including longer duration of mechanical ventilation, longer time to first meconium passage, and higher mean airway pressure levels, were more common in the infusion versus bolus dose only group [1]. Follow-up in 78 newborns (39 in both the fentaNYL and placebo groups) at 2 years of corrected age demonstrated a significant decrease in eye and hand coordination skills in the newborns administered fentaNYL continuous infusion versus bolus only. No difference was demonstrated for locomotor, personal and social skills, hearing and language, and performance [5].
Anesthesia.
Sedation.

Administration

Intravenous: For continuous infusion, further dilute in compatible solution to a concentration of 10 mcg/mL. For intermittent infusions, administer over 15 to 30 minutes at concentrations of 10 mcg/mL [3].
Alternative concentrations for continuous infusion include undiluted (50 mcg/mL) solution, or further dilution in compatible solution to a concentration of 2, 4, 5, 10, 25 mcg/mL [4].

MEDICATION SAFETY

Contraindications/Precautions

Precautions
Addiction: Abuse, misuse, or opioid addiction may occur; increased risk in patients with a personal or family history of substance abuse or mental illness; monitoring recommended [6]
Cardiovascular: Bradyarrhythmias may occur; monitoring recommended, particularly when initiating therapy [6]
Cardiovascular: Severe hypotension, including orthostatic hypotension and syncope, may occur in ambulatory patients, especially those with decreased blood volume or concurrent use of CNS depressants (eg, phenothiazides, general anesthetics). Avoid use in patients with circulatory shock [6].
Cardiovascular: Increased blood pressure may occur when coadministered with a neuroleptic agent; monitoring recommended [6].
Concomitant use: Avoid use with mixed agonists/antagonists and partial agonist analgesics [6]
Concomitant use: Use not recommended within 14 days of MAOI administration [6]
Concomitant Use: Potentially life-threatening serotonin syndrome may occur with concomitant use of serotonergic drugs. In general, symptom onset occurs within several hours to a few days of concomitant use, but may occur later [6].
Endocrine: Adrenal insufficiency, typically with more than 1 month of use, has been reported. If adrenal insufficiency is suspected, perform diagnostic testing, treat with corticosteroids if confirmed, wean patient off of opioid if appropriate, and continue to assess adrenal function [6].
Gastrointestinal: Spasm of sphincter of Oddi may occur. Serum amylase may increase; monitoring recommended [6].
Hepatic: Biliary tract disease, including acute pancreatitis; use may cause spasm of the sphincter of Oddi and exacerbate symptoms; monitoring recommended [6]
Hepatic: Clearance may be decreased in patients with hepatic impairment; dose adjustments recommended in patients with mild to moderate hepatic impairment ; monitoring recommended [6]
Hepatic: Avoid use in patients with severe hepatic impairment [6].
Neurologic: Increased frequency of seizures may occur; monitoring recommended [6].
Neurologic: Decreased respiratory drive and subsequent carbon dioxide retention may

occur, which may further increase intracranial pressure in susceptible patients (eg, brain tumors, elevated intracranial pressure); monitoring recommended especially at initiation [6]
Neurologic: Avoid use in patients with coma or impaired consciousness; opioids may obscure clinical course of head injury [6]
Musculoskeletal: Dose-related and rate-of-administration-related muscular rigidity, particularly involving muscles of respiration, has been reported with fentanyl injection; management protocol advised [7]
Renal: Clearance may be decreased in patients with renal impairment ; dose adjustments as needed ; monitoring recommended [6]
Respiratory: Decreased respiratory drive or apnea may occur in patients with chronic pulmonary disease (eg, chronic obstructive pulmonary disease, cor pulmonale, those with decreased respiratory reserve, hypoxia, hypercapnia, or respiratory depression); monitoring recommended, especially when given with other agents which depress respiration; consider nonopioid alternatives [6]
Respiratory: Sleep-related breathing disorders including central sleep apnea and sleep-related hypoxemia may occur and risk increases in a dose-dependent fashion; dose reduction may be necessary [6]
Respiratory: Cachectic, or debilitated patients have an increased risk for respiratory depression; monitoring recommended, especially when given with other agents which depress respiration; consider nonopioid alternatives [6]
Withdrawal: Serious withdrawal symptoms, including uncontrolled pain, psychological distress, and suicide, may occur upon sudden dose decrease or discontinuation in patients who are physically dependent on opioid medications; do not discontinue abruptly and create a patient-specific plan to taper the opioid gradually [8].

Adverse Effects

Respiratory depression occurs when anesthetic doses (greater than 5 mcg/kg) are used and may also occur unexpectedly because of redistribution. Chest wall rigidity has occurred in 4% of neonates who received 2.2 to 6.5 mcg/kg per dose, occasionally associated with laryngospasm. This was reversible with administration of naloxone. Urinary retention may occur when using continuous infusions. Tolerance may develop to analgesic doses with prolonged use. Significant withdrawal symptoms have been reported in patients treated with continuous infusion for 5 days or longer.

Black Box Warning

Warnings: Addiction, abuse, and misuse; live-threatening respiratory depression; CYP450 3A4 interaction; and risks from concomitant use of benzodiazepines or other CNS depressants [6]

- **Addiction, Abuse, and Misuse**
- Fentanyl exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing, and monitor regularly for

these behaviors or conditions.

- **Life-threatening Respiratory Depression**
- Serious, life-threatening, or fatal respiratory depression may occur. Monitor for respiratory depression, especially during initiation of fentanyl or following a dose increase. Because of the risk of respiratory depression, fentanyl is contraindicated for use as an as-needed analgesic, in non-opioid tolerant patients, in acute pain, and in postoperative pain.
- **Cytochrome P450 3A4 Interaction**
- The concomitant use of fentanyl with all cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in fentanyl plasma concentration. Monitor patients receiving fentanyl and any CYP3A4 inhibitor or inducer.
- **Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants**
- Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.
- Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation.

Solution Compatibility

D_5W, and NS.

Terminal Injection Site Compatibility

fentaNYL undiluted at 50 mcg/mL:
Acetaminophen (10 mg/mL), acyclovir (5 mg/mL and 7 mg/mL), aminocaproic acid (20 mg/mL), amphotericin B lipid complex (1 mg/mL), amphotericin B liposome (1 mg/mL), anidulafungin (0.5 mg/mL), argatroban (1 mg/mL), bivalirudin (5 mg/mL), calcium gluconate (100 mg/mL), caspofungin (0.5 mg/mL and 0.7 mg/mL), cefazolin (20 mg/mL), cefotaxime (20 mg/mL), cefuroxime (15 mg/mL and 30 mg/mL), cimetidine (15 mg/mL), clindamycin (9 mg/mL), clonidine (18 mcg/mL), dactinomycin (10 mcg/mL), dexamethasone (4 mg/mL), dexmedetomidine (4 mcg/mL), digoxin (0.1 mg/mL), diltiazem (1 mg/mL), dobutamine (2 mg/mL and 4 mg/mL), dolasetron (2 mg/mL), dopamine (1.6 mg/mL and 3.2 mg/mL), epinephrine (20 mcg/mL), esmolol (10 mg/mL), etomidate (2 mg/mL), foscarnet (24 mg/mL), furosemide (10 mg/mL), gentamicin (10 mg/mL), granisetron (50 mcg/mL), heparin (1 unit/mL and 100 units/mL), hydrocortisone succinate (10 mcg/mL), hydromorphone (1 mg/mL), labetalol (2 mg/mL), lansoprazole (0.55 mg/mL), levofloxacin (5 mg/mL), linezolid

(2 mg/mL), lorazepam (0.33 mg/mL and 0.5 mg/mL), methotrexate (15 mg/mL), metronidazole (5 mg/mL), midazolam (2 mg/mL and 5 mg/mL), milrinone (0.2 mg/mL and 0.4 mg/mL), morphine (2 mg/mL), mycophenolate mofetil (6 mg/mL), nafcillin (33 mg/mL), nitroglycerin (0.2 mg/mL and 0.4 mg/mL), nicardipine (0.1 mg/mL), norepinephrine (0.128 mg/mL), octreotide (5 mcg/mL), ondansetron (1 mg/mL), palonosetron (50 mcg/mL), piperacillin/tazobactam (40/5 mg/mL), potassium chloride (0.04 mEq/mL), propofol (10 mg/mL and 20 mg/mL), quinupristin/dalfopristin (5 mg/mL), ranitidine (1 mg/mL), rocuronium (1 mg/mL), sargramostim (6 mcg/mL and 15 mcg/mL), sodium bicarbonate (1 mEq/mL), tacrolimus (20 mcg/mL), theophylline (1.6 mg/mL), tobramycin (10 mg/mL), vancomycin (5 mg/mL), vecuronium (1 mg/mL), and voriconazole (4 mg/mL).

fentaNYL diluted to 40 mcg/mL:

Midazolam (0.1 mg/mL)

fentaNYL diluted to 30 mcg/mL:

Esomeprazole (0.32 mg/mL).

fentaNYL diluted to 25 mcg/mL:

Amikacin (20 mg/mL), aminophylline (12.5 mg/mL), atracurium (5 mg/mL), atropine (0.4 mg/mL and 0.5 mg/mL), azathioprine (13.3 mg/mL), aztreonam (80 mg/mL), bretylium (40 mg/mL), bumetanide (0.125 mg/mL), calcium chloride (50 mg/mL), calcium gluconate (50 mg/mL), cefazolin (220 mg/mL), cefotaxime (285 mg/mL), cefotetan (400 mg/mL), cefoxitin (450 mg/mL), ceftazidime (400 mg/mL), ceftriaxone (165 mg/mL), cefuroxime (125 mg/mL), chloramphenicol (333 mg/mL), cimetidine (24 mg/mL), clindamycin (48 mg/mL), cyclosporine (2 mg/mL), dexamethasone (1 mg/mL and 12 mg/mL), digoxin (0.125 mg/mL), diphenhydramine (2 mg/mL and 25 mg/mL), dobutamine (6.25 mg/mL), dopamine (12.8 mg/mL), doxycycline (4 mg/mL), enalaprilat (0.625 mg/mL), epinephrine (0.5 mg/mL), epoetin alfa (5000 units/mL), erythromycin (20 mg/mL), esmolol (40 mg/mL), famotidine (5 mg/mL), fluconazole (2 mg/mL), furosemide (5 mg/mL), ganciclovir (40 mg/mL), gentamicin (6.4 mg/mL), heparin (160 units/mL), hydrocortisone succinate (62.5 mg/mL), imipenem/cilastatin (5 mg/mL), indomethacin (1 mg/mL), insulin (50 units/mL), isoproterenol (80 mcg/mL), ketorolac (1 mg/mL and 15 mg/mL), labetalol (2.5 mg/mL), lidocaine (10 mg/mL), lorazepam (0.1 mg/mL), magnesium sulfate (250 mg/mL), mannitol (150 mg/mL), methyldopate (25 mg/mL), methylprednisolone (125 mg/mL), metoclopramide (2.5 mg/mL and 5 mg/mL), metoprolol (0.5 mg/mL), midazolam (0.2 mg/mL and 2.5 mg/mL), morphine (4 mg/mL), nafcillin (250 mg/mL), nalbuphine (10 mg/mL), naloxone (16 mcg/mL), netilmicin (50 mg/mL), nitroglycerin (1.6 mg/mL), nitroprusside (0.8 mg/mL), norepinephrine (0.5 mg/mL), ondansetron (1 mg/mL), oxacillin (160 mg/mL), papaverine (15 mg/mL), penicillin G potassium (500,000 units/mL), penicillin G sodium (500,000 units/mL), pentobarbital (25 mg/mL), phenobarbital (2 mg/mL and 65 mg/mL), phentolamine (5 mg/mL), phenylephrine (4 mg/mL), phytonadione (5 mg/mL), potassium chloride (1 mEq/mL), procainamide (250 mg/mL), propranolol (0.5 mg/mL), protamine (5 mg/mL), pyridoxine (50 mg/mL), quinidine gluconate (40 mg/mL), ranitidine (2 mg/mL), sodium bicarbonate (0.5 mEq/mL), succinylcholine (8 mg/mL), theophylline (4 mg/mL), ticarcillin/clavulanate (195 mg/mL), tobramycin (6.4 mg/mL), vancomycin (20 mg/mL), vasopressin (4 units/mL), and verapamil (1.25 mg/mL).

fentaNYL diluted to 20 mcg/mL:

Midazolam (0.1 mg/mL and 0.5 mg/mL).

fentaNYL diluted to 12.5 mcg/mL:

Cisatracurium (0.1 mg/mL, 2 mg/mL, and 5 mg/mL), and remifentanil (25 mcg/mL and 0.25 mg/mL).

fentaNYL diluted to 10 mcg/mL:

Alprostadil (7.5 mcg/mL), atracurium (0.5 mg/mL), pancuronium (50 mcg/mL), propofol (10

and 20 mg/mL), and vecuronium (0.1 mg/mL.
fentaNYL diluted to 2 mcg/mL:
Enalaprilat (50 mcg/mL).

Terminal Injection Site Incompatibility

Didiazoxide, pantoprazole, phenytoin, and sulfamethoxazole/trimethoprim.

Monitoring

Monitor respiratory and cardiovascular status closely. Observe for abdominal distention, loss of bowel sounds, and muscle rigidity.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Synthetic opioid narcotic analgesic that is 50 to 100 times more potent than morphine on a weight basis. Extremely lipid soluble. Penetrates the CNS rapidly. Transient rebound in fentaNYL serum concentration may reflect sequestration and subsequent release of fentaNYL from body fat. Metabolized extensively in the liver by CYP 3A4 enzyme system and then excreted by the kidney. Highly protein bound (80% to 85%). Apparent volume of distribution is approximately 4.5 L/kg in infants, decreasing to 3 L/kg in children. Distribution half-life of 3 to 5 minutes. Higher clearance and longer half-life in infants (less than 12 months of age) compared with children and adults [9][10][11][12][13].

Concentrations
FentaNYL $AUC_{0 \text{ to } 24}$ was 19.6 mcg x hr/L (interquartile range (IQR) 10.4, 33.5) for boluses of 1 mcg/kg/dose IV every 4 hours and 13.2 mcg x hr/L (IQR 10.8, 22.6) (p=0.12) for continuous infusion of 1 mcg/kg/hr IV administered fentaNYL for analgesia and sedation during mechanical ventilation (n=100). The median trough concentration was 0.41 to 0.97 ng/mL for the bolus dosing and the median serum fentaNYL concentration was 0.42 to 0.61 ng/mL for the continuous infusion. At all time points for both groups the pain scores demonstrated adequate relief of both acute and ongoing pain. The need for additional sedatives or analgesics were comparable between groups. The mean gestational age was 35.4 weeks for the bolus group and 36.5 weeks for the infusion group. The majority of infants were younger than 1 week (85.1% in the bolus group and 90.6% in the infusion group) [14].

Clearance: 4.1 L/hr (IQR 2, 6.4 L/hr) in 53 infants (median age 1 week; gestational age (GA) 36.5 weeks) administered fentanyl 1 mcg/kg/hr [14]

Half-life: 8.4 hours (IQR 7.9, 9.7 hr) in 53 infants (median age 1 week; gestational age (GA) 36.5 weeks) administered fentanyl 1 mcg/kg/hr and 26.7 hours (IQR 8.1, 65.2 hours; p=0.002) in 47 infants (median age 2 weeks; GA 35.4 weeks) administered 1 mcg/kg/dose IV every 4 hours [14]

ABOUT

Special Considerations/Preparation

Available: 2-, 5-, 10-, and 20-mL ampules in a concentration of 50 mcg/mL [15]. A 10-mcg/mL dilution may be made by adding 1 mL of the 50-mcg/mL concentration to 4 mL preservative-free normal saline.

Stability

At least 95% of the original concentration of fentaNYL remained on day 100 when fentaNYL 10 mcg/mL (0.01 mg/mL) in NS or D5W and fentaNYL 50 mcg/mL (0.05 mg/mL) were stored at room temperature in polypropylene syringes [16].

Ferrous sulfate

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

2 mg/kg/day of elemental iron for growing premature infants. **(Maximum of 15 mg/day)**.
Begin therapy after 2 weeks of age.

Infants with birthweights less than 1000 grams may need 4 mg/kg/day.

6 mg/kg/day of elemental iron for patients receiving erythropoietin.
Administer orally in 1 or 2 divided doses, preferably diluted in formula.

Uses

Iron supplementation for prevention and treatment of anemia.

MEDICATION SAFETY

Adverse Effects

Nausea, constipation, black stools, lethargy, hypotension, and erosion of gastric mucosa.

Monitoring

Monitor hemoglobin and reticulocyte counts during therapy.
Observe stools, check for constipation.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Well absorbed from stomach.

ABOUT

Special Considerations/Preparation

Drops: Ferrous sulfate drops available as 15 mg elemental iron per 1 mL (0.2% alcohol). **Confirm product concentration.**
Elixir: Contains 44 mg elemental iron per 5 mL (some with 5% alcohol).

Flecainide

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Tachyarrhythmias unresponsive to conventional therapies
Begin at 2 mg/kg per dose every 12 hours orally. Adjust dose based on response and serum concentrations to a maximum of 4 mg/kg per dose every 12 hours. Correct preexisting hypokalemia or hyperkalemia before administration. Optimal effect may take 2 to 3 days of therapy to achieve, and steady-state plasma levels may not be reached until 3 to 5 days at a given dosage in patients with normal renal and hepatic function. Therefore, do not increase dosage more frequently than approximately once every 4 days.

Uses

Treatment of supraventricular arrhythmias not responsive to conventional therapies. Not recommended in patients with structurally abnormal hearts.

Administration

Infant formulas and milk may decrease absorption. If milk is removed from the infant's diet, a reduction in dose should be considered [1][2][3].

MEDICATION SAFETY

Contraindications/Precautions

Contraindicated in patients with preexisting second- or third-degree AV block, or with right bundle branch block when associated with a left hemiblock, unless a pacemaker is present. Also contraindicated in the presence of cardiogenic shock [1].

Adverse Effects

Flecainide can cause new or worsened arrhythmias, including AV block, bradycardia,

ventricular tachycardia, torsades de pointes. There is also a negative inotropic effect. Dizziness, blurred vision, and headache have been reported in children.

Black Box Warning

An excessive mortality or non-fatal cardiac arrest rate was seen in patients (adults) with asymptomatic non-life-threatening ventricular arrhythmias and a history of myocardial infarction treated with flecainide compared with that seen in patients assigned to a carefully matched placebo-treated group in the Cardiac Arrhythmia Suppression Trial (CAST). It is prudent to consider the risks of Class IC agents (including flecainide), coupled with the lack of any evidence of improved survival, generally unacceptable in patients without life-threatening ventricular arrhythmias, even if the patients are experiencing unpleasant, but not life-threatening, symptoms or signs. Flecainide is not recommended for use in patients with chronic atrial fibrillation. Case reports of ventricular proarrhythmic effects in patients treated with flecainide for atrial fibrillation/flutter have included increased PVCs, VT, ventricular fibrillation (VF), and death.

Monitoring

Continuous EKG during initiation of therapy, as this is the most common time to see drug-induced arrhythmias. Follow trough serum concentrations closely at initiation, 3 to 5 days after any dose change, and with any significant change in clinical status or diet. Therapeutic trough levels are 200 to 800 nanograms/mL.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Flecainide is a class IC antiarrhythmic that produces a dose-related decrease in intracardiac conduction in all parts of the heart, thereby increasing PR, QRS and QT intervals. Effects upon atrioventricular (AV) nodal conduction time and intra-atrial conduction times are less pronounced than those on the ventricle. Peak serum concentrations occur 2 to 3 hours after an oral dose. Infant formula and milk products interfere with drug absorption. Plasma protein binding is about 40% in adults and is independent of plasma drug level. Children under 1 year of age have elimination half-life values of 11 to 12 hours. Elimination half-life in newborns after maternal administration is as long as 29 hours.

ABOUT

Special Considerations/Preparation

Available: 50-mg, 100-mg, and 150-mg tablets.

Extemporaneous Compounds
5 mg/mL Oral Suspension: An oral suspension with a final concentration of 5 mg/mL can be made as follows: crush 6 (six) 100-mg tablets, slowly mix in 20 mL of a 1:1 mixture of Ora-Sweet® and Ora-Plus®, or cherry syrup (cherry syrup concentrate diluted 1:4 with simple syrup) to form a uniform paste, then add to this mixture enough vehicle to make a final volume of 120 mL. Shake well and protect from light. Stable for 45 days refrigerated and at room temperature when stored in amber glass or plastic [4].

20 mg/mL Oral Solution: [5].

- Add 2000 mg of pure pharmaceutical grade flecainide powder to a 250 mL beaker
- Add 50 mL of purified water that has been heated to 37°C to the beaker
- While maintaining temperature at 37°C, mix the solution, using magnetic stirring, until the solution is transparent (10 minutes). Temperature should not exceed 37°C.
- Transfer to a 100 mL graduated cylinder.
- Wash the beaker with approximately 10 mL of simple syrup and transfer to the graduated cylinder.
- Add sufficient volume of simple syrup to the graduated cylinder for a final volume of 100 mL.
- Transfer back to the beaker for 10 minutes to homogenize the mixture using magnetic stirring.
- Transfer to an amber bottle.
- Stable for 30 days at 25°C

20 mg/mL Oral Suspension: An oral suspension with a final concentration of 20 mg/mL may also be compounded. Extemporaneously compounded flecainide acetate 20 mg/mL prepared in either a 1:1 mixture of Ora-Sweet® and Ora-Plus®, a 1:1 mixture of Ora-Sweet SF® and Ora-Plus®, or cherry syrup (cherry syrup concentrate diluted 1:4 with simple syrup) and placed in a 120-mL amber polyethylene terephthalate bottle is stable, retaining a mean of at least 92% of the initial drug concentration, for up to 60 days when stored without light at 5 and 25 degrees C [6].

Fluconazole

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Coccidioidomycosis: 6 to 12 mg/kg/day IV or orally; continue empiric therapy until infection can be ruled out [1].

Invasive Candidiasis: 12 to 25 mg/kg loading dose, then 6 to 12 mg/kg per dose IV, or orally [2][3][4][5]. In neonates and children, a dose of 12 mg/kg/day is recommended. Duration of therapy for candidemia, without metastatic complications, is 2 weeks after documented clearance of *Candida* from the bloodstream and resolution of symptoms [6]. Consider the higher doses for treating severe infections or *Candida* strains with higher MICs (4 to 8 mcg/mL). Extended dosing intervals should be considered for neonates with renal insufficiency (serum creatinine greater than 1.3 mg/dL).
Higher doses may be required in patients receiving extracorporeal membrane oxygenation (ECMO) [7].
Note: The higher loading and maintenance doses are based on pharmacokinetic/pharmacodynamic data but have not been prospectively tested for efficacy or safety.

Antibiotic Dosing Chart:

Invasive Candidiasis Dosing Interval Chart		
Gest. Age (weeks)	**PostNatal (days)**	**Interval (hours)**
≤29	0 to 14 >14	48 24
30 and older	0 to 7 >7	48 24

Invasive Candidiasis; Prophylaxis (birth weight less than 1000 g [6]**or less than 1500 g):**[8] 3 to 6 mg/kg/dose IV or orally twice weekly for 6 weeks in neonatal intensive care units with high incidence rates of *Candida* infections [8][6].

Candidemia, receiving ECMO:
Birth to 3 months postnatal age, gestational age younger than 30 weeks: 35 mg/kg orally/IV as a loading dose, followed by maintenance dose of 9 mg/kg orally/IV once daily for at least 3 weeks and for at least 2 weeks following resolution of symptoms [9][10]
Birth to 3 months postnatal age, gestational age 30 weeks or older: 35 mg/kg orally/IV as a loading dose, followed by maintenance dose of 12 mg/kg orally/IV once daily for at least 3 weeks and for at least 2 weeks following resolution of symptoms [9][10]

Candidiasis, receiving ECMO:
Birth to 3 months postnatal age, gestational age younger than 30 weeks: 35 mg/kg

orally/IV as a loading dose, followed by maintenance dose of 9 mg/kg orally/IV once daily for at least 3 weeks and for at least 2 weeks following resolution of symptoms [9][10]
Birth to 3 months postnatal age, gestational age 30 weeks or older: 35 mg/kg orally/IV as a loading dose, followed by maintenance dose of 12 mg/kg orally/IV once daily for at least 3 weeks and for at least 2 weeks following resolution of symptoms [9][10]

Thrush: 6 mg/kg on Day 1, then 3 mg/kg per dose every 24 hours orally.
Dose Adjustments
There are no data available for neonates with renal impairment; however, the following dose adjustments are based on recommendations for adults with renal impairment [11]:
For patients with renal impairment: The normal loading dose should be given, followed by a reduced daily dose [12].
For patients with a CrCl of 50 mL/min or less (no dialysis): The daily dose should be reduced by 50% [12].
For patients receiving dialysis: 100% of the usual dose should be given after each dialysis session; on non-dialysis days, patients should receive a reduced dose according to creatinine clearance [11].

Uses

Treatment of systemic infections, meningitis, and severe superficial mycoses caused by *Candida* species. Resistance has been reported with *C glabrata* and *C krusei* and in patients receiving long-term suppressive therapy.

Neonatal Candidiasis, Including CNS Infection[6]
Invasive candidiasis and candidemia, or very low-birth weigh infants with asymptomatic candiduria .

- Amphotericin B deoxycholate is recommended.
- Fluconazole IV or oral is an alternative for those who have not been receiving prophylaxis with fluconazole.
- Lipid formulation amphotericin B agent is an alternative; however use with caution, especially in the presence of urinary tract involvement.
- Echinocandins (caspofungin, anidulafungin, or micafungin) should be limited to salvage therapy or scenarios of resistance or toxicity to amphotericin B deoxycholate or fluconazole

Central nervous system infections

- Amphotericin B deoxycholate is recommended.
- Liposomal amphotericin B is an alternative.
- Salvage therapy with flucytosine may be added in those patients who have not responded to initial therapy.
- Fluconazole may be used as step-down therapy for fluconazole-susceptible isolates in those patients who respond to initial therapy

Neonatal intensive care unit (with greater than 10% rate of invasive candidiasis)[6]

- Prophylaxis with IV or oral fluconazole for 6 weeks is recommended for neonates with birth weights of less than 1000 g
- Prophylaxis with oral nystatin is an alternative in neonates with birth weights of less than 1500 g when fluconazole is unavailable or fluconazole resistance is present

Prophylaxis of invasive candidiasis: One recommendation is to limit the use of prophylactic fluconazole to high-risk premature infants when the rate of invasive candidiasis is greater than 2% to 5% [14]. The odds of invasive candidiasis (OR 0.2 (95% CI, 0.08 to 0.51) and *Candida* colonization (OR 0.28 (95% CI, 0.18 to 0.41) occurred less often in the fluconazole compared with placebo group in an evaluation of 4 trials of prophylaxis in premature infants in the United States. Mortality was not different (11% for fluconazole and 14% for placebo). There was no difference between groups in adverse events (ALT, AST, alkaline phosphatase, or conjugated bilirubin levels). Resistance to *Candida* isolates were not different between the groups [8].
Further evidence suggest prophylactic fluconazole be limited to when the incidence is moderate to high (specific incidence not identified). Although fluconazole prophylaxis reduced the rates of invasive candidiasis (3% vs 9% (p=0.02)), it did not reduce the primary outcome of incidence of death or invasive candidiasis in infants weighing less than 750 g (median, 25 weeks gestation and 120 hours or younger) compared with placebo in a multicenter study (n=361). The dose of oral or IV fluconazole was 6 mg/kg/dose twice weekly for 42 days [15]. The duration of treatment is important; the overall combined relative risks of invasive fungal infection were 0.8 (95% CI, 0.48 to 1.35) with a 28-day treatment and 0.3 (95% CI, 0.15 to 0.58) with a 42-day treatment of prophylactic fluconazole in a meta-analysis (5 studies; 1006 preterm neonates with birthweight less than 1500 g) [16].

Coccidioidomycosis: Empiric fluconazole is recommended for neonates born to mothers with coccidioidomycosis. Discontinue fluconazole once coccidioidomycosis has been ruled out [1].

Administration

Intravenous: Infuse at concentration of 2 mg/mL over 1 to 2 hours **(maximum rate 200 mg/hour)**. Solutions for intravenous infusion are supplied premade (glass bottle or Viaflex® plastic bag) in a concentration of 2 mg/mL [12].

In the preparation and administration of injections, National Institute for Occupational Safety and Health (NIOSH) recommends the use of double gloves and a protective gown. Prepare in a biological safety cabinet or a compounding aseptic containment isolator; eye/face and respiratory protection may be needed. Prepare compounds in a closed system drug transfer device. During administration, if there is a potential that the substance could splash or if the patient may resist, use eye/face protection. Administer certain dosage forms via a closed system drug transfer device [13].

Oral: May be given with or without food [12].

The National Institute for Occupational Safety and Health (NIOSH) recommends the use of single gloves by anyone handling intact tablets or capsules or administering from a unit-dose package [13].
In the preparation of tablets or capsules, including cutting, crushing, or manipulating, or the handling of uncoated tablets, NIOSH recommends the use of double gloves and a protective gown. Prepare in a ventilated control device, if possible. Use respiratory protection if not prepared in a control device. During administration, wear single gloves, and wear eye/face protection if the formulation is hard to swallow or if the patient may resist, vomit, or spit up [13].
NIOSH recommends the use of double gloves and a protective gown by anyone handling a hazardous oral liquid or preparing any hazardous drug for administration via a feeding tube. Prepare in a control device, if possible. Use respiratory, eye, and face protection if not done in a control device. During administration, eye/face protection is needed if the patient may resist, or if there is potential to vomit or spit up [13].

MEDICATION SAFETY

Contraindications/Precautions

Contraindicated in patients receiving **cisapride**, due to precipitation of life-threatening arrhythmias [12][18]; **terfenadine**, in patients receiving multiple doses of fluconazole 400 mg or higher; and **QT-prolonging drugs metabolized by CYP3A4** (eg, **astemizole**, **cisapride**, **erythromycin**, **pimozide**, or **quinidine**) [19].
Cardiovascular: QT prolongation and torsade de pointes have been reported rarely, primarily in seriously ill patients with multiple confounding risk factors such as structural heart disease, electrolyte abnormalities, and concomitant medications; additional caution advised with use in patients with potentially proarrhythmic conditions [20]
Cardiovascular: Increased risk of life-threatening ventricular arrhythmias and torsades de pointes in patients with hypokalemia and advanced cardiac failure [20]
Concomitant use: Narrow therapeutic index drugs that are metabolized by CYP2C9 or CYP3A4; monitoring recommended [19]
Concomitant use: Avoid voriconazole [19]
Dermatologic: Exfoliative skin disorders have been reported rarely with some fatal cases reported in patients with serious underlying diseases [19]
Endocrine and metabolic: Adrenal insufficiency, including reversible cases, have been reported [17]
Hepatic: Hepatic toxicity, including fatalities, has been reported rarely; monitoring recommended and discontinue if signs of liver disease develop [19]
Hepatic: Use caution in patients with liver dysfunction due to increased risk of hepatic toxicity; monitoring recommended and discontinue if condition worsens [19]
Immunologic: Use caution in patients with hypersensitivity to other azole antifungal agents; cross-hypersensitivity not yet determined [19]
Immunologic: Anaphylaxis has been reported rarely [19]
Immunologic: Deep seated fungal infection and presence of rash; monitoring recommended and discontinue if lesions progress [19]
Immunologic: Superficial fungal infection; discontinue if rash occurs and is attributed to

drug [19]
Renal: Preexisting renal dysfunction [19]
Special populations: Sucrase-isomaltase deficiency or heredity fructose or glucose/galactose malabsorption; avoid powder for oral suspension as it contains sucrose [19]

Adverse Effects

Common: Vomiting (5%), abdominal pain (3%), nausea (2%), and diarrhea (2%) with fluconazole in doses up to 15 mg/kg/day for a maximum of 1616 days (n=577; age range, 1 day to 17 years) [17].

Hepatic Mean AST at 4 weeks was significantly greater with fluconazole prophylaxis (16.8 units/L) compared with placebo (13.1 units/L) while mean ALT was not significantly different between fluconazole and placebo groups (22.8 units/L vs 19.5 units/L), in a randomized, double-blind trial of 322 very-low-birth-weight infants. No clinical signs of hepatotoxicity or cholestasis were observed. No treatment for cholestasis or phototherapy for hyperbilirubinemia was required. Prophylactic fluconazole doses were 3 or 6 mg/kg/dose every third day for the first 2 weeks, then every other day for a total duration of 6 weeks for extremely-low-birth-weight infants and for a total duration of 4 weeks for neonates weighing 1000 to 1500 g [21].
Conjugated hyperbilirubinemia (greater than 2 mg/dL) occurred significantly more frequently in extremely-low-birth-weight (ELBW) infants with fluconazole prophylaxis (42.9%; n=140) compared with that of ELBW infants not given fluconazole prophylaxis (8.8%; n=137), in a retrospective study with historical controls. Prolonged duration of conjugated hyperbilirubinemia and treatment with ursodeoxycholic acid was performed more often in the fluconazole group. At discharge, the rate of conjugated hyperbilirubinemia was similar between groups. Fluconazole dosage was 3 mg/kg/dose every 72 hours for 2 weeks, then every 48 hours for 2 weeks, then every day for 2 weeks [22].

Monitoring

Monitor for more serious hepatic injury in patients who develop abnormal liver function tests during therapy [17].
For candidemia, monitor blood cultures daily or every other day until *Candida* is cleared [6].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action: Water-soluble triazole antifungal agent. Inhibits cytochrome P450-dependent ergosterol synthesis [11].

Drug Concentrations
AUC: A median 25-mg/kg IV loading dose followed by median 18.6 mg/kg/day (range 9.3 to 21.5 mg/kg/day) IV attained a median $AUC_{0 \text{ to } 24}$ of 898.2 (95% CI, 503.4 to 1445.7) mg x hr/L at steady state in 18 neonates with suspected or confirmed systemic candidiasis. Postnatal age was a median of 13.5 days (range, 2 to 101 days; median gestational age was 28 weeks + 2 days) [23].

ADME
Absorption: Well absorbed after oral administration (90% bioavailability), with peak serum concentrations reached within 1 to 2 hours [17].
Distribution: Less than 12% protein binding. Good penetration into CSF after both oral and IV administration; CSF concentrations are approximately 80% of the corresponding plasma concentrations [17].
Volume of Distribution: Median 0.913 L/kg (95% CI, 0.913 to 0.913 L/kg) in 18 neonates a median age of 13.5 days (range, 2 to 101 days; median gestational age 28 weeks + 2 days)[23].
Metabolism: Fluconazole is a potent inhibitor of CYP2C19 and is a moderate inhibitor of CYP3A4 and CYP2C9 [17].
Excretion: Primarily excreted unchanged in the urine [17].
Clearance: In premature neonates (26 to 29 weeks gestational age), 0.18 mL/min/kg within 36 hours of birth, 0.218 mL/min/kg 6 days later, and 0.333 mL/min/kg 12 days later. In infants 9 months of age to children 13 years of age, clearance was 0.4 to 0.51 mL/min/kg after a single oral dose [17].
Median clearance was 0.015 L/hr/kg (95% CI, 0.008 to 0.039 L/hr/kg) in 18 neonates a median age of 13.5 days (range, 2 to 101 days; median gestational age 28 weeks + 2 days)[23].
Half-life: In premature neonates (26 to 29 weeks gestational age), 73.6 hours within 36 hours of birth, 53.2 hours 6 days later, and 46.6 hours 12 days later. In infants 9 months of age to children 13 years of age, half-life was 19.5 to 25 hours after a single oral dose [17].
Median half-life was 40.9 hours (95% CI, 16.2 to 78.4 hours) in 18 neonates a median 13.5 days of age (range, 2 to 101 days; median gestational age 28 weeks + 2 days) [23]

ABOUT

Special Considerations/Preparation

Injection
Available as a premixed solution for IV injection in concentrations of 200 mg/100 mL and 400 mg/200 mL in Viaflex® bags or glass bottles (2 mg/mL). Do not remove overwrap from Viaflex® bag until ready for use. **Store at room temperature.Do not freeze**.

Oral
Oral dosage form is available as a powder for suspension in concentrations of 10 mg/mL and

40 mg/mL. Prepare both concentrations by adding 24 mL distilled water to bottle of powder and shaking vigorously. Each bottle will deliver 35 mL of suspension. Suspension is stable at room temperature for 2 weeks. **Do not freeze**.

Extemporaneous compound: For a 1 mg/mL suspension, pulverize 5 100-mg tablets in a mortar and add deionized water to make a suspension. Transfer liquid to a graduate and add sufficient additional water to final volume of 500 mL. May store at room temperature or under refrigeration (preferable); stable for 15 days. Shake well before using [24][25].

Safe handling: The National Institute for Occupational Safety and Health (NIOSH) recommends the use of double gloves and a protective gown by anyone compounding a hazardous oral liquid or preparing any hazardous drug for administration by feeding tube. If possible, prepare in a control device. Respiratory, eye, and face protection are needed if not done in a control device [13].

Flucytosine

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

12.5 to 37.5 mg/kg per dose every 6 hours orally. Increase dosing interval if renal dysfunction is present.

Uses

Antifungal agent used in combination with amphotericin B or fluconazole for treatment of infections caused by *Candida, Cryptococcus,* and other sensitive fungi.

MEDICATION SAFETY

Contraindications/Precautions

Contraindications
Known complete dihydropyrimidine dehydrogenase (DPD) enzyme deficiency [1]

Precautions
Endocrine and metabolic: Patients with dihydropyrimidine dehydrogenase deficiency (DPD) are at an increased risk of severe drug toxicity (eg, mucositis, diarrhea, neutropenia, and neurotoxicity). Determination may be considered where drug toxicity is confirmed or suspected; consider discontinuation in the event of suspected drug toxicity [1]
Hematologic: Use extreme caution in patients with bone marrow depression; patients who have a hematologic disease or are receiving or have received treatment with radiation or medications which depress bone marrow may be more susceptible [1].
Hematologic: Bone marrow toxicity may occur and may be irreversible or can lead to death in immunosuppressed patients; monitoring recommended [1].

Adverse Effects

Toxicities are related to serum concentration above 100 mcg/mL, and are usually reversible if the drug is stopped or the dose is reduced. Fatal bone marrow depression (related to fluorouracil production), hepatitis, severe diarrhea, rash. Amphotericin B may increase toxicity by decreasing renal excretion.

Black Box Warning

Use with extreme caution in patients with impaired renal function. Close monitoring of hematologic, renal and hepatic status of all patients is essential. These instructions should be thoroughly reviewed before administration of flucytosine [1].

Monitoring

Desired peak serum concentration ranges from 50 to 80 mcg/mL. Assess renal function. Follow GI status closely. Twice-weekly CBC and platelet counts. Periodic AST, ALT.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Well absorbed orally. Transformed within cell to fluorouracil, which interferes with RNA synthesis. Excellent penetration into CSF and body tissues. 90% renal elimination of unchanged drug, proportional to GFR. Serum half-life in adults is 3 to 5 hours if renal function is normal, but 30 to 250 hours if renal impairment is present. Limited pharmacokinetic data in premature infants. Resistance develops frequently if used alone. Synergistic with amphotericin even if treating resistant strain.

ABOUT

Special Considerations/Preparation

Flucytosine is available as 250- and 500-mg capsules. A pediatric suspension (10 mg/mL) may be prepared by mixing contents of four 250-mg capsules with enough vehicle (1:1 mixture of Ora-Sweet® (or Ora-Sweet SF®) and Ora-Plus® or cherry syrup) to make a final volume of 100 mL. Suspension is stable for 60 days at room temperature or under refrigeration. Shake well before use and **protect from light**.

A 50-mg/mL suspension may be prepared by mixing six 500-mg capsules with enough vehicle (1:1 mixture of Ora-Plus® and Ora-Sweet NF® (or other syrup)) to make a final volume of 60 mL. Suspension is stable for at least 90 days when stored at room temperature or under refrigeration. Shake well before use.

Flumazenil

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

IV: 5 to 10 mcg/kg/dose IV over 15 seconds. May repeat every 45 seconds until the patient is awake. Maximum total cumulative dose should not exceed 50 mcg/kg (0.05 mg/kg) or 1 mg in infants, whichever is smaller (data in infants older than 1 year). No reported maximum dose in neonates has been tested.

Intranasal: 40 mcg/kg/dose divided equally between both nostrils. Administer via TB syringe for accurate equal dosing.

Rectal: 15 to 30 mcg/kg/dose, may repeat if sedation not reversed within 15 to 20 minutes.

Uses

Reversal of sedative effect from benzodiazepines, in cases of suspected benzodiazepines overdose, and in neonatal apnea secondary to prenatal benzodiazepine exposure.

Administration

Intravenous: Administer 0.1 mg/mL (100 mcg/mL) as an IV bolus injection over 15 seconds through a free flowing intravenous infusion into a large vein [1].

Rectal: Has been administered undiluted through a short, air-washed cannula in children [2].

MEDICATION SAFETY

Adverse Effects

The reported experience in neonates is very limited. Use with caution in neonates with preexisting seizure disorders. Hypotension has been reported in adults following rapid administration. Resedation has been reported in 10% of treated pediatric patients, occurring 19 to 50 minutes after initial dosing. May cause pain on injection. Observe IV site for extravasation.

Black Box Warning

According to the manufacturer's black box warning, the use of flumazenil has been associated with the occurrence of seizures. Seizures are most frequent in patients who have been on benzodiazepines for long-term sedation.

Solution Compatibility

D_5W, Lactated Ringer's, and NS.

Terminal Injection Site Compatibility

Aminophylline, cimetidine, dobutamine, dopamine, famotidine, heparin, lidocaine, procainamide, and ranitidine.

Monitoring

Monitor for the return of sedation and respiratory depression. Continuous EKG and blood pressure.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Imidazobenzodiazepine that is a benzodiazepine receptor antagonist. Competitively inhibits the activity at the benzodiazepine recognition site on the GABA/benzodiazepine receptor. Eliminated rapidly by hepatic metabolism to three inactive metabolites. Highly lipid soluble and penetrates the brain rapidly. Elimination half-life in children 20 to 75 minutes. Peak concentration reached in 3 minutes when delivered intravenously (children). Limited pharmacokinetic data in neonates.

ABOUT

Special Considerations/Preparation

Available in an injectable form as a 0.1 mg/mL concentration in 5- and 10-mL multidose vials. If drawn into a syringe or mixed with D_5W, LR, or NS, discard solution after 24 hours. Discard opened vials within 24 hours. Store at room temperature. Injectable preparation may be given intranasally or rectally.

Folic Acid

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Adequate Intake:
65 mcg/day orally or enterally [1].

Enteral Nutrition
Preterm: 25 to 50 *mcg/kg/day* orally [1]; **MAX 65 mcg/day**.
Term: 65 *mcg/day* orally [1].

Parenteral Nutrition
Preterm: 56 *mcg/kg/day* IV; **MAX 140 mcg/day for infants 3 kg or more; 91 mcg/day for infants 1 to 3 kg; and 42 mcg for infants less than 1 kg**. Multivitamin formulations (140 mcg/5 mL): 5 mL for infants 3 kg or more; 3.25 mL for infants 1 to 3 kg, and 1.5 mL for infants less than 1 kg [1]
Term: 140 *mcg/day* IV [1].

Supplementation During Breast-feeding:
50 mcg (0.05 mg) orally, IV, IM, or subQ every day in infants who are breast-fed by mothers with folic acid deficiency [2].

Uses

Supplementation may be needed in low-birth-weight infants, in infants who are breast-fed by a mother with folic acid deficiency, infants with infections, or infants with prolonged diarrhea [2].

Administration

May administer as IM, IV, or subQ injection; oral route is preferred [3].

MEDICATION SAFETY

Contraindications/Precautions

Contraindications[2]
- Previous intolerance to the drug

Precautions
Administration: Higher than recommended doses (above 0.1 mg/day) may obscure pernicious anemia [3][2]
Benzyl alcohol: Parenteral product contains benzyl alcohol which has been associated with fatal gasping syndrome in premature infants [3]
Hematologic: Folic acid monotherapy is not sufficient for treatment of pernicious anemia or other megaloblastic anemias when vitamin B_{12} is deficient [3][2].
Toxicity: Aluminum toxicity may occur with prolonged parenteral administration, particularly in premature neonates and in patients with impaired renal function. Parental doses of aluminum greater than 4 to 5 mcg/kg/day may result in CNS or bone toxicity [3]

Adverse Effects

Allergic sensitization has occurred with both oral and parenteral administration of folic acid [3][2].

Solution Compatibility

D_5W, NS

Terminal Injection Site Compatibility

Alfentanil hydrochloride (0.25 mg/mL), aminophylline (12.5 mg/mL), ascorbic acid injection (250 mg/mL), atracurium besylate (5 mg/mL), atropine sulfate (0.5 mg/mL), azathioprine sodium (13.33 mg/mL), aztreonam (80 mg/mL), benztropine mesylate (0.5 mg/mL), bretylium tosylate (40 mg/mL), bumetanide (0.125 mg/mL), calcium gluconate (50 mg/mL), cefamandole nafate (333 mg/mL), cefazolin sodium (220 mg/mL), cefoperazone (80 mg/mL), cefotaxime (285 mg/mL), cefotetan disodium (400 mg/mL), cefoxitin (450 mg/mL), ceftazidime (400 mg/mL), ceftizoxime (400 mg/mL), ceftriaxone sodium (165 mg/mL), cefuroxime (125 mg/mL), chloramphenicol sodium succinate (333 mg/mL), cimetidine hydrochloride (24 mg/mL), clindamycin phosphate (48 mg/mL), cyanocobalamin (0.5 mg/mL), cyclosporine (2 mg/mL), dexamethasone sodium phosphate (12 mg/mL), digoxin (0.125 mg/mL), diphenhydramine hydrochloride (25 mg/mL), dopamine hydrochloride (12.8 mg/mL), enalaprilat (0.625 mg/mL), ephedrine sulfate (12.5 mg/mL), epinephrine hydrochloride (0.5 mg/mL), epoetin alfa (5000 units/mL), erythromycin lactobionate (20 mg/mL), esmolol hydrochloride (40 mg/mL), famotidine (0.2 mg/mL), fentanyl citrate (25 mcg/mL), fluconazole (2 mg/mL), furosemide (5 mg/mL), ganciclovir sodium (40 mg/mL), glycopyrrolate (0.1 mg/mL), heparin sodium (160 units/mL). hydrocortisone sodium

succinate (62.5 mg/mL), hydroxyzine hydrochloride (25 mg/mL), imipenem-cilastatin sodium (5 mg/mL), indomethacin sodium trihydrate (1 mg/mL), insulin regular (50 units/mL), ketorolac tromethamine (15 mg/mL), labetalol hydrochloride (2.5 mg/mL), Lactated Ringer's Injection, lidocaine hydrochloride (10 mg/mL), magnesium sulfate (250 mg/mL), mannitol (150 mg/mL), meperidine hydrochloride (50 mg/mL), methylprednisolone sodium succinate (125 mg/mL), metoclopramide hydrochloride (2.5 mg/mL), metoprolol tartrate (0.5 mg/mL), midazolam hydrochloride (2.5 mg/mL), multiple vitamins injection (0.08 mL/mL), naloxone hydrochloride (16 mcg/mL), nitroglycerin (1.6 mg/mL), nitroprusside sodium (0.8 mg/mL), ondansetron hydrochloride (1 mg/mL), oxacillin sodium (160 mg/mL), oxytocin (0.08 unit/mL), penicillin G potassium (500,000 units/mL), penicillin G sodium (500,000 units/mL), pentobarbital sodium (25 mg/mL), phenobarbital sodium (65 mg/mL), phentolamine mesylate (5 mg/mL), phenylephrine hydrochloride (4 mg/mL), phytonadione (5 mg/mL), piperacillin sodium (320 mg/mL), potassium chloride (1 mEq/mL), procainamide hydrochloride (250 mg/mL), propranolol hydrochloride (0.5 mg/mL), ranitidine hydrochloride (2 mg/mL), Ringer's injection, sodium bicarbonate (0.5 mEq/mL), streptokinase (80,000 units/mL), succinylcholine chloride (8 mg/mL), sufentanil citrate (25 mcg/mL), theophylline (4 mg/mL), ticarcillin disodium (345 mg/mL), ticarcillin disodium/clavulanate potassium (195 mg/mL), urokinase (50,000 units/mL), vancomycin hydrochloride (20 mg/mL), vasopressin (4 units/mL)

Terminal Injection Site Incompatibility

Amikacin sulfate, calcium chloride, chlorpromazine hydrochloride, dantrolene sodium, diazepam, diazoxide, dobutamine hydrochloride, doxycycline hyclate, gentamicin sulfate, haloperidol lactate. hydralazine hydrochloride, inamrinone lactate, isoproterenol hydrochloride, metaraminol bitartrate, methyldopate hydrochloride, minocycline hydrochloride, morphine sulfate, nafcillin sodium, nalbuphine hydrochloride, netilmicin sulfate, norepinephrine bitartrate, pentamidine isethionate, pentazocine lactate, phenytoin sodium, prochlorperazine edisylate, promethazine hydrochloride, protamine sulfate, pyridoxine hydrochloride, sulfamethoxazole-trimethoprim, tacrolimus, thiamine hydrochloride, tobramycin sulfate, tolazoline hydrochloride, verapamil hydrochloride

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action

Folic acid is the precursor of tetrahydrofolic acid, which is a cofactor for transformylation reactions in the biosynthesis of purines and thymidylates of nucleic acids. Impairment of thymidylate synthesis is thought to account for the defective DNA synthesis which leads to megaloblast formation and megaloblastic and macrocytic anemias [2].

Folic acid stimulates the production of red blood cells, white blood cells, and platelets in persons suffering from megaloblastic anemias [3].

Absorption
Folic acid is rapidly absorbed from the small intestine, primarily from the proximal portion. [2].
Tmax: 1 hour, generally [2].

Distribution
CSF concentrations are several times greater than serum concentrations (16 to 21 mg/mL compared to 5 to 15 mg/mL) [2]

Metabolism
Folic acid is metabolized in the liver to 7,8-dihydrofolic acid and eventually to 5,6,7,8-tetrahydrofolic acid with the aid of reduced diphosphopyridine nucleotide and folate reductases [2].

Excretion
Kidney: Following a single oral dose of 100 mcg, only a trace amount of folic acid is detected in the urine. With oral doses of 5 mg and 40 mcg/kg, approximately 50% of the dose was detected in the urine. Similarly, after a single oral dose of 15 mg, up to 90% of the dose was recovered in the urine. Most metabolites appeared in the urine after 6 hours in most cases and excretion was generally complete within 24 hours [2].
Other: Small amounts of orally administered folic acid appear in the feces. Folic acid is excreted in milk of lactating mothers [2].

ABOUT

Special Considerations/Preparation

Oral Route
Availability: 1-mg [2], and OTC products, 0.8- and 0.4-mg tablets and 5-mg and 20- mg (20,000 mcg) capsules.
Storage: Store at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F) [2].

Extemporaneous Oral Liquid (1 mg/mL)
- Heat 90 mL of purified water to almost boiling
- Dissolve 200 mg of methylparaben and 20 mg of propylparaben in the heated water
- Cool the solution to room temperature
- Dissolve 100 mg of folic acid in the solution
- Add sufficient quantity of sodium hydroxide 10% solution to adjust pH of 8 to 8.5
- Add sufficient purified water to for a final volume of 100 mL and mix well

The beyond-use date is 30 days [4].

Parenteral Route
Availability: 50 mg/10 mL (5 mg/mL). Contains benzyl alcohol 15 mg/mL [3]. Multivitamin

formulations contain 140 mcg/5 mL of folic acid.
Storage: Store at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F) [3].

Fosphenytoin

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Note: Fosphenytoin dosing is expressed in phenytoin sodium equivalents (PE). (Fosphenytoin 1 mg PE = phenytoin sodium 1 mg) [1].

Seizure (short-term administration when oral phenytoin is not possible)
Same total daily phenytoin sodium equivalents (PE) dose as oral phenytoin sodium dose, given IM or IV. Should generally not be given IM in pediatric patients [2].

Seizure, During Neurosurgery; Treatment and Prophylaxis
Loading Dose: 10 to 15 mg PE/kg IV (**1 to 2 mg PE/kg per minute; maximum 150 mg PE/minute** whichever is slower). May be administered by the IM route but the IV route is preferred [2].
Maintenance Dose: 2 to 4 mg PE/kg/dose IV (**1 to 2 mg PE/kg per minute; maximum 100 mg PE/minute** whichever is slower) every 12 hours. May be administered by the IM route but the IV route is preferred [2].

Status Epilepticus
Loading Dose: 15 to 20 mg PE/kg IV (**no faster than 2 mg PE/kg per minute; maximum 150 mg PE/minute** whichever is slower)[3]; 20 mg PE/kg IV was the most common loading dose in a review of 11 clinical protocols for treatment of neonatal seizure [4]. May be administered by the IM route but the IV route is preferred [2].
Maintenance Dose: 2 to 4 mg PE/kg/dose IV (**1 to 2 mg PE/kg per minute; maximum 100 mg PE/minute** whichever is slower) every 12 hours. May be administered by the IM route but the IV route is preferred [2]. The most common maintenance doses were 8 to 10 mg PE/kg/day IV (range, 5 to 10 mg PE/kg/day) in a review of 11 clinical protocols for treatment of neonatal seizure [4].

Dosage Adjustment
Pharmacogenomics
CYP2C9 intermediate or poor metabolizer: Reduce dose. No specific recommendations in pediatric patients; in adults the starting maintenance dose should be reduced by at least 25% in intermediate metabolizers and at least 50% in poor metabolizers. Dose adjustments are based on target phenytoin concentrations [5].
HLA-B*15:02 carrier: If phenytoin-naive, do not use [5].
HLA-B*15:02 noncarrier with normal CYP2C9 genotype: No dosage adjustment necessary [5].

Uses

Anticonvulsant
Fosphenytoin was recommended when escalation to a second-line anti-seizure medication was indicated 30 to 60 minutes after a second phenobarbital dose in a review of 11 clinical protocols for treatment of neonatal seizures. Expert opinion was split between use of fosphenytoin or levetiracetam as the second-line agent of choice [4].

Pediatric FDA Approved Indications
Indicated for the treatment of generalized tonic-clonic status epilepticus and prevention and treatment of seizures occurring during neurosurgery in all pediatric age groups. May be used as a short-term substitute for oral phenytoin in patients with seizure disorders and should only be used when oral phenytoin administration is not possible [2].

Administration

Do not confuse concentration of fosphenytoin with the total amount of drug in the vial. Dosing errors have occurred, with patients receiving 2- or 10- fold overdoses of fosphenytoin, including fatal outcomes [2].

Intravenous: Administer 1 to 2 mg PE/kg per minute **(maximum 150 mg PE/minute for loading dose and 100 mg PE/minute for maintenance dose)** at a concentration of 1.5 to 25 mg PE/mL [2]. Some institutions use standard concentrations of 10 mg PE/mL and 25 mg PE/mL [6].
Intramuscular: Administer undiluted. May divide dose and give in more than one site [1][7][8].
IM administration of fosphenytoin should not ordinarily be used for status epilepticus due to delays in achieving a therapeutic concentration compared with IV administration [9].

In the preparation and administration of injections, the National Institute for Occupational Safety and Health (NIOSH) recommends the use of double gloves and a protective gown. Prepare in a biological safety cabinet or a compounding aseptic containment isolator; eye/face and respiratory protection may be needed. Prepare compounds in a closed system drug transfer device. During administration, if there is a potential that the substance could splash or if the patient may resist, use eye/face protection. Administer certain dosage forms via a closed system drug transfer device [10].

MEDICATION SAFETY

Contraindications/Precautions

Contraindications
- Adams-Stokes syndrome [12]
- Concomitant use with delavirdine [12]
- Hypersensitivity to fosphenytoin, any other product components, phenytoin, or other hydantoins [13]

• History of prior acute hepatotoxicity attributable to fosphenytoin sodium or phenytoin [2]
• Second and third degree atrioventricular block [12]
• Sino-atrial block [12]
• Sinus bradycardia [12]

Precautions
Alcohol use: Acute alcohol use may increase phenytoin concentrations while chronic alcohol use may decrease concentrations [12].
Cardiovascular: Increased risk of cardiovascular reactions, including severe hypotension and cardiac arrhythmias (ie, bradycardia, heart block, QT interval elongation, ventricular tachycardia, and ventricular fibrillation) which have resulted in asystole, cardiac arrest, and death, have been associated with rapid administration; increased risk in critically ill, elderly and patients with hypotension and severe myocardial insufficiency. Use oral therapy whenever possible; monitoring is required and decreased rate of or drug discontinuation may be needed [13].
Cardiovascular: Cardiac events have been reported in adults and children without underlying cardiac disease or comorbidities, and at recommended doses and infusion rates. Use oral therapy whenever possible; monitoring required and administration rate reduction or discontinuation may be needed [13].
Dermatologic: Severe cutaneous reactions, including fatalities [eg, acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN)] have been reported ; discontinue use at the first sign of rash, unless clearly not drug-related, and evaluate patients for severe cutaneous reaction; do not reinitiate therapy if signs or symptoms suggest severe cutaneous reaction [13].
Dermatologic: Patients with the HLA-B*1502 allele and/or CYP2C9*3 carriers (more common in patients of Asian ancestry) may have increased risk of developing serious cutaneous adverse reactions (eg, SJS and TEN); consider avoiding phenytoin as a carbamazepine alternative in patients with these genetic variations [13].
Dermatologic: Edema, discoloration, and pain distal to injection site "purple glove syndrome") have been reported following peripheral IV injection, which may or may not be associated with extravasation, and may present several days after administration [12].
Endocrine and metabolic: Consider phosphate load (0.0037 mmol phosphate/mg PE fosphenytoin sodium) in patients requiring phosphate restriction, including severe renal impairment [12].
Endocrine and metabolic: May increase fosphenytoin clearance to phenytoin without corresponding phenytoin clearance increase in patients with hypoalbuminemia, which may potentiate frequency and severity of adverse effects; monitoring of unbound phenytoin serum levels is recommended [12]
Endocrine and metabolic: Hyperglycemia has been reported [12].
Hematologic: Hematopoietic events (eg, thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, and pancytopenia with or without bone marrow suppression), including fatal cases, have been reported [12].
Hematologic: May be associated with exacerbation of porphyria; use with caution in patients with this disease [12].
Hematologic: May lower serum folate levels [12].
Hepatic: May increase fosphenytoin clearance to phenytoin without corresponding phenytoin clearance increase in patients with hepatic disease, which may potentiate frequency and severity of adverse effects; monitoring of unbound phenytoin serum levels is recommended [12]
Hepatic: Hepatotoxicity (eg, jaundice, hepatomegaly, elevated serum transaminase levels,

leukocytosis, eosinophilia, and acute hepatic failure), some cases fatal, has been reported; immediately discontinue use and do not readminister [12].
Immunologic: Angioedema has been reported; discontinue immediately for presence of symptoms (ie, facial, perioral, or upper airway swelling) [13].
Immunologic: Drug reaction with eosinophilia and systemic symptoms (DRESS), also known as multiorgan hypersensitivity, including fatal cases, has been reported; immediately evaluate if suspected and discontinue use if confirmed [12].
Immunologic: In patients with phenytoin hypersensitivity, consider alternative to structurally similar drugs such as carboxamides (e.g., carbamazepine), barbiturates, succinimides, and oxazolidinediones (eg, trimethadione); if there is a personal or family history of hypersensitivity to structurally similar drugs, consider alternative therapy [12].
Immunologic: Lymphadenopathy, including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's disease, has been reported; extended monitoring required and discontinuation recommended [11].
Medication safety: Medication errors, some resulting in death with 10-fold overdoses, have occurred; the amount of drug to be given in phenytoin equivalents (mg PE) should not be confused with the concentration of the drug in the vial; carefully examine and confirm correct dose before administering [12].
Neurologic: Abrupt discontinuation may increase seizure frequency or precipitate status epilepticus; dose reduction or discontinue should occur gradually when possible [12].
Neurologic: Delirium, psychosis, encephalopathy, and rarely irreversible cerebellar dysfunction and/or atrophy may occur with phenytoin levels sustained above the therapeutic range; monitoring is recommended, and dosage adjustment or discontinuation may be necessary [12].
Neurologic: Not approved for absence seizures or seizures due to hypoglycemic or other metabolic causes [12]
Renal: May increase fosphenytoin clearance to phenytoin without corresponding phenytoin clearance increase in patients with renal disease, which may potentiate frequency and severity of adverse effects; monitoring of unbound phenytoin serum levels is recommended [12]
Reproductive: May cause fetal harm [2]
Special populations: Patients with impaired liver function and the gravely ill may show early signs of toxicity [12].
Special populations: Avoid use in HLA-B*15:02 carriers if patient is phenytoin/fosphenytoin-naive [5]. HLA-B*1502-positive patients (most common in Asian patients) may have an increased risk of Stevens-Johnson syndrome and toxic epidermal necrolysis [12].
Special populations: Avoid using as an alternative for carbamazepine in HLA-B*1502-positive patients [12].
Special populations: Dose reduction and monitoring recommended in HLA-B*15:02 non-carriers with intermediate or poor CYP2C9 metabolizer status [5].

Adverse Effects

Fewer infusion-related reactions and tissue damage (eg, purple glove syndrome) compared with phenytoin. Hypotension and cardiac arrhythmias have been reported. Dose related adverse events include nystagmus (total level, 15 to 25 mg/L) and ataxia and mental status

changes (total level greater than 30 mg/L). Movement disorders (bradykinesia and choreoathetosis) may also occur rarely. Minor venous irritation upon IV administration. Vomiting is common in children. Long-term effects of therapy include gingival hyperplasia, coarsening of the facies, hirsutism, hyperglycemia, and hypoinsulinemia. Fosphenytoin drug interactions are similar to phenytoin (ie, carbamazepine, cimetidine, corticosteroids, digoxin, furosemide, phenobarbital, and valproate) [14][15].
Use with caution in infants and children with hyperbilirubinemia: both fosphenytoin and bilirubin displace phenytoin from protein-binding sites, resulting in increased serum free phenytoin concentration [16].

Serious and sometimes fatal skin reactions, including Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis, have been reported with phenytoin therapy. Onset of symptoms is typically within 28 days, but can occur later. Limited data suggests that a particular human leukocyte antigen (HLA) allele, HLA-B*1502, found in patients of Asian ancestry may be a risk factor for the development of SJS/TEN in patients taking phenytoin. Consideration should be given to avoiding phenytoin as an alternative for carbamazepine in patients positive for HLA-B*1502 [17]. Because fosphenytoin is a prodrug and is converted to phenytoin after administration, any concern regarding this association is also applicable to fosphenytoin.

Black Box Warning

The rate of intravenous fosphenytoin administration should not exceed 150 mg phenytoin sodium equivalents (PE) per minute because of the risk of severe hypotension and cardiac arrhythmias. Careful cardiac monitoring is needed during and after administering intravenous fosphenytoin. Although the risk of cardiovascular toxicity increases with infusion rates above the recommended infusion rate, these events have also been reported at or below the recommended infusion rate. Reduction in rate of administration or discontinuation of dosing may be needed [12].

Solution Compatibility

D_5W, $D_{10}W$ and NS.

Terminal Injection Site Compatibility

Lorazepam, phenobarbital, and potassium chloride.

Terminal Injection Site Incompatibility

Midazolam.

Monitoring

Therapeutic Laboratory Monitoring

• Measure serum phenytoin concentrations (the active metabolite of fosphenytoin) to guide dosage adjustment and achievement of target therapeutic concentrations (reference range, 10 to 20 mcg/mL [40 to 79 mcmol/L]; unbound phenytoin, 1 to 2 mcg/mL). Peak concentrations are best evaluated no sooner than 2 hours after the end of IV infusion or 4 hours after an IM injection to capture full conversion of fosphenytoin to phenytoin and may aid in determining an individual's threshold for dose-related side effects. Measure trough levels just prior to the next scheduled dose [2].
• Monitor unbound phenytoin levels in patients with renal or hepatic impairment, and in those with hypoalbuminemia [2].
• Monitor unbound phenytoin levels periodically during pregnancy (because of potential changes in protein binding) [2].

Toxic Laboratory Monitoring

• Measure serum phenytoin level immediately at first sign of acute toxicity (eg, confusion, delirium, psychosis, encephalopathy) [2].
• Monitor phenytoin serum levels when a drug interaction is suspected [2].
• Measure unbound phenytoin levels in patients with renal or hepatic impairment, and in those with hypoalbuminemia [2].
• Monitor unbound phenytoin serum levels periodically during pregnancy (due to potential changes in protein binding) as a guide to appropriate dosage adjustment [2].
• Monitor for signs and symptoms of hyperammonemia during concomitant use of valproate [11].

Toxic Physical Monitoring

• Carefully monitor ECG, blood pressure, and respiratory function continuously during IV administration and throughout the period where maximal serum phenytoin concentrations occur (ie, approximately 10 to 20 minutes after the end of the infusion), especially in elderly or critically ill patients and those with hypotension and severe myocardial insufficiency [2].
• Monitor for signs and symptoms of hyperammonemia during concomitant use of valproate [11].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action: Fosphenytoin, a prodrug, exerts its anticonvulsant effects when converted to phenytoin. At the cellular level, phenytoin is responsible for modulating voltage-dependant sodium and calcium channels and enhancement of sodium-potassium ATPase activity. The anticonvulsant activity is primarily attributed to the modulation of sodium

channels [1].

Therapeutic Drug Concentrations
AUC
IV, single-dose, 400 to 1200 mg (PE): Total and free phenytoin AUC increased disproportionately to dose [1]
Time to peak concentration
IM, fosphenytoin sodium (prodrug): 30 minutes [1]
IM, phenytoin (active drug): 1.5 to 3 hours [1]
IV, fosphenytoin sodium (prodrug): At the end of infusion [1]
Therapeutic concentration
Seizure disorder: 10 to 20 mcg/mL (measured as phenytoin) [1]
Hepatic disease: Increased fraction of unbound phenytoin [12]
Renal disease: Increased fraction of unbound phenytoin [12]
Hypoalbuminemia: Increased fraction of unbound phenytoin [12]

Absorption
Bioavailability
IM: Complete [1]

Distribution
Protein binding
Fosphenytoin, plasma proteins: 95% to 99% (primarily to albumin) [1]
Phenytoin, plasma proteins: 70% to 88% (primarily to albumin) [1]

Metabolites
Phenytoin (Major): Active [1]
Phosphate (Major): Inactive [1]
Formaldehyde (Major): Inactive [1]

Excretion
Renal excretion
Fosphenytoin (prodrug): None [1]
Phenytoin (active drug): Primarily excreted in urine (1% to 5% unchanged) [1]
Total body
Renal or hepatic disease or hypoalbuminemia: Fosphenytoin clearance to phenytoin may be increased without a similar increase in phenytoin clearance [12]

Elimination Half-Life
Parent compound
Fosphenytoin (prodrug): 15 minutes [1]
Elimination metabolites
Phenytoin (active drug): 12 to 28.9 hours [1]

Fosphenytoin is a water-soluble prodrug of phenytoin rapidly converted by phosphatases in blood and tissue. It has no known intrinsic pharmacologic activity before conversion to phenytoin. Each 1.5 mg of fosphenytoin is metabolically converted to 1 mg phenytoin. Nonlinear (zero order) kinetics (as dose increases, saturation of elimination mechanisms occur leading to progressive accumulation of phenytoin). After IV administration, peak concentration is reached at end of infusion. After IM administration, peak is reached in

approximately 20 to 30 minutes. Conversion half-life of fosphenytoin administered intravenously to infants and children is approximately 8 minutes. No drugs have been identified to interfere with the conversion of fosphenytoin to phenytoin. Fosphenytoin is highly protein bound (adults 95% to 99%); only free fraction can cross blood-brain barrier. Primarily eliminated through hepatic metabolism. Potent inducer of cytochrome P450 enzyme systems resulting in a reduction of serum levels of drugs metabolized by this system. Renal excretion is negligible. Serum half-life reflects that of phenytoin (18 to 70 hours) due to rapid conversion. The conversion of fosphenytoin to phenytoin yields very small amounts of formaldehyde and phosphate. This is only significant in cases of large overdosage. Phenytoin serum concentrations measured up to two hours after IV and four hours after IM dose may be falsely elevated due to fosphenytoin interaction with immunoanalytic methods (eg, TDx fluorescence polarization) [14][15][18][19][20][8].

ABOUT

Special Considerations/Preparation

Cerebyx®
Availability: Injectable solution in a concentration equivalent to 50 mg PE/mL, in 2- and 10-mL vials. Administer IM undiluted. Administer IV after diluting in NS or D_5W to a concentration of 1.5 to 25 mg PE/mL. The pH is 8.6 to 9 [1].
Storage: Refrigerate vials between 2 and 8 degrees C (36 and 46 degrees F). Solution may be kept at room temperature for up to 48 hours. For single use only; discard unused product [1].
Phosphate load: Provides 0.0037 mmol phosphate/mg PE [1].

Furosemide

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Initial Dose: 1 mg/kg IV, IM, or orally.
May increase to a maximum of 2 mg/kg/dose IV or 6 mg/kg/dose orally.
Initial Intervals:
Premature infant: every 24 hours.
Full-term infant: every 12 hours.
Full-term infant older than 1 month: every 6 to 8 hours.
Consider alternate-day therapy for long-term use.

Uses

Chronic lung disease, adjunct: Diuretic that may also improve pulmonary function [2]. Based on results from a systematic review of the use of furosemide in infants with (or developing) chronic lung disease (CLD), furosemide was associated with no or inconsistent effects on lung function in preterm infants less than 3 weeks of age. For preterm infants greater than 3 weeks of age with CLD, single IV doses were associated with short-term (less than 1 hour) improvement in lung compliance and airway resistance. Infants receiving chronic diuretic therapy had improved oxygenation and lung compliance. There are no data to support the routine or sustained use of loop diuretics based on duration of ventilatory support, duration of hospitalization, long-term outcomes, or survival in infants with CLD [3][4].

Heart Failure: In neonates with pulmonary hypertension, supportive care with diuretics may be used cautiously for signs of right-sided heart failure [5].

Posthemorrhagic ventricular dilation (PHVD), adjunct; Prevention of shunt placement: Use of acetazolamide and furosemide in preterm infants with PHVD was associated with a higher rate of shunt placement, death, and increased neurological morbidity as compared to standard therapy alone, in a multicenter, randomized, controlled trial (n=177). Infants less than 3 months beyond the expected date of delivery and with a ventricular width more than 4 mm above the 97th percentile after intraventricular hemorrhage received either standard therapy plus acetazolamide 100 mg/kg daily and furosemide 1 mg/kg daily (n=88) or standard therapy alone (n=89). Mean gestational age was 28.5 weeks and median postnatal age was 23.5 days in the drug therapy group. Median treatment duration of acetazolamide was 35 days. Assessments at 1 year showed that death or shunt placement had occurred in 56 infants (63.3%) in the drug therapy group and in 46 (52.2%) allocated to standard therapy (11.1% (CI, -3.2% to 25.2%; p=0.15). Adverse effects were reported in 38 infants; 23 of whom required permanent discontinuation of drug therapy [6]. In a small cohort study, 9 of 10 preterm infants with raised intracranial

hypertension secondary to PVHD treated with acetazolamide and furosemide avoided the placement of ventriculoperitoneal shunt; in comparison, 3 of 6 patients who received serial lumbar puncture avoid shut placement. Acetazolamide was started at 20 mg/kg/day and increased by 10 mg/kg up to 100 mg/kg/day in 3 divided doses administered orally or if necessary, IV; dose of furosemide was 1 mg/kg daily orally or IV. Mean gestational age was 28.4 weeks. [7]. Limited use of acetazolamide may be warranted in infants with PVHD and raised intracranial hypertension based on the findings of Kennedy et al, 2001 [6].

Administration

Administer a 2 to 10 mg/mL concentration of furosemide over 15 to 30 minutes [1].

MEDICATION SAFETY

Contraindications/Precautions

Contraindications:
Anuria [10].
History of hypersensitivity to furosemide [10]

Cardiovascular: Increased risk of persistent patent ductus arteriosis when administrated to premature infants during first week of life [10]
Concomitant use: Avoid aminoglycosides [10]
Concomitant use: Ethacrynic acid not recommended [10]
Endocrine and metabolic: Preexisting electrolyte depletion should be corrected prior to treatment [10]
Endocrine and metabolic: Excessive diuresis may cause dehydration and blood volume reduction with circulatory collapse and possibly vascular thrombosis and embolism [10]
Endocrine and metabolic: Electrolyte imbalance, including hyponatremia, hypochloremic alkalosis, hypokalemia, hypomagnesemia, and hypocalcemia, may occur especially in patients receiving higher doses and a restricted salt intake; monitoring recommended [10]
Endocrine and metabolic: Hypokalemia has been reported, especially with brisk diuresis, inadequate electrolyte intake, cirrhosis, or concomitant use with corticosteroids, ACTH, large amounts of licorice, or prolonged use of laxatives [10]
Endocrine and metabolic: Blood glucose increases, alterations in glucose tolerance tests, or precipitation of diabetes have been reported [10]
Endocrine and metabolic: Asymptomatic hyperuricemia or gout may occur [10]
Hematologic: Blood dyscrasias may occur; monitoring recommended [10]
Hepatic: Hepatic damage may occur; monitoring recommended [10]
Hepatic: Patients with preexisting hepatic cirrhosis and ascites may experience precipitated hepatic coma with sudden fluid or electrolyte alteration; strict monitoring recommended [10]
Hepatic: Not recommended in patients with preexisting hepatic coma until basic condition is improved [10]
Immunologic: Patients with preexisting systemic lupus erythematosus may be at risk for

exacerbation or activation [10]
Immunologic: Patients with sulfonamide allergy are at increased risk of furosemide allergy [10]
Otic: Ototoxicity, including tinnitus, reversible/irreversible hearing impairment, and deafness, has been reported especially with rapid injection (infusion rate not to exceed 4 mg/min in adults), severe renal impairment, higher than recommended doses, hypoproteinemia, or concomitant ototoxic drugs such as aminoglycosides and ethacrynic acid [10]
Otic: Hearing loss has been associated with furosemide injection in neonates [11]
Renal: Renal damage may occur; monitoring recommended [10]
Renal: Use caution in patients with preexisting severe progressive renal disease; discontinue if azotemia and oliguria worsen [10]
Renal: Nephrocalcinosis or nephrolithiasis may be precipitated in premature infants and may also occur in children under 4 years without prematurity receiving chronic therapy; monitoring recommended [10]
Renal: Severe urinary retention increases risk of acute urinary retention particularly during initial stages of treatment; monitoring recommended [10]
Renal: Patients at high-risk for radiocontrast nephropathy may experience higher incidence of renal deterioration [10]
Renal: Patients with hypoproteinemia (associated with nephrotic syndrome) may experience reduced efficacy and increased risk of ototoxicity [10]

Adverse Effects

Endocrine and metabolic: Furosemide therapy may lead to increased hyponatremia and a significant rise in serum creatinine in patients receiving indomethacin for PDA closure [12][13].
Otic: After adjusting for risk factors and severity of illness, no association was demonstrated between prolonged furosemide (at least 28 days duration) and hearing screen failure in a cohort of premature infants from the Pediatrix Medical Group. The absolute difference in hearing screen failure between those exposed (n=1020) and those not exposed (n=790) to furosemide was 3% (95% CI, -0.2% to 6.2%) [14].
Renal: Nephrocalcinosis and nephrolithiasis may occur due to high urinary calcium excretion. This has been reported mainly in premature infants and a cumulative dose of 10 mg/kg or greater was associated with an increased risk [8]. Cases have also occurred in infants with no history of prematurity; monitoring recommended [15].
Hypercalciuria and development of bone demineralization and renal calculi occur with long-term therapy. May displace bilirubin from albumin binding sites when given in high doses or for prolonged periods. Cholestatic jaundice and cholelithiasis have also been reported with loop diuretics (mainly in preterm infants receiving long-term TPN and furosemide therapy. [16][17][18][19][20]

Black Box Warning

Furosemide is a potent diuretic which, if given in excessive amounts, can lead to profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is

required and dose and dose schedule must be adjusted to the individual patient's needs [10].

Solution Compatibility

NS, D_5W, $D_{10}W$, and sterile water for injection.

Terminal Injection Site Compatibility

Amikacin, aminophylline, amiodarone, ampicillin, atropine, aztreonam, bumetanide, calcium gluconate, cefepime, ceftazidime, cimetidine, dexamethasone, digoxin, epinephrine, famotidine, fentanyl, heparin, hydrocortisone succinate, ibuprofen lysine, indomethacin, lidocaine, lorazepam, linezolid, meropenem, micafungin, morphine, nitroglycerin, penicillin G, piperacillin/tazobactam, potassium chloride, propofol, prostaglandin E_1, ranitidine, remifentanil, sodium bicarbonate, sodium nitroprusside, and tobramycin.

Terminal Injection Site Incompatibility

Azithromycin, caspofungin, ciprofloxacin, dobutamine, dopamine, erythromycin lactobionate, esmolol, fluconazole, gentamicin, hydralazine, isoproterenol, metoclopramide, midazolam, milrinone, netilmicin, nicardipine, and vecuronium.

Monitoring

Monitor serum and urine electrolytes and renal function periodically during therapy. Consider performing renal ultrasonography in premature infants as furosemide may precipitate nephrocalcinosis/nephrolithiasis [8]. Follow serum potassium levels closely at initiation, in patients receiving concomitant diuretics or digoxin, and during long-term therapy. Monitor urine output and weight changes. Monitor for signs/symptoms of fluid/electrolyte imbalance [9].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

The diuretic actions of furosemide are primarily at the ascending limb of Henle's loop, and are directly related to renal tubular drug concentration. Furosemide causes major urinary losses of sodium, potassium, and chloride. Urinary calcium and magnesium excretion, and

urine pH are also increased. Prostaglandin production is stimulated, with increases in renal blood flow and renin secretion. Free water clearance is increased and CSF production is decreased by weak carbonic anhydrase inhibition. Nondiuretic effects include decreased pulmonary transvascular fluid filtration and improved pulmonary function. Protein binding is extensive, but bilirubin displacement is negligible when using normal doses. Oral bioavailability is good. Time to peak effect when given IV is 1 to 3 hours; duration of effect is approximately 6 hours, although half-life may be as long as 67 hours in the most immature neonates.

ABOUT

Special Considerations/Preparation

Availability: Oral solution 8-mg/mL and 10-mg/mL; injection 10 mg/mL concentration in 2-, 4-, and 10-mL single use vials.
Storage: Protect from light. Store at 25 degrees C; excursions permitted to 15 to 30 degrees C (59 to 86 degrees F). For the oral solution, discard open bottle after 90 days [15][21].

Compounded IV Solutions
1 mg/mL solution: 1 mL of 10-mg/mL injectable solution was added to 9 mL of D_5W for injection resulting in a 1 mg/mL furosemide solution. When stored in polypropylene syringes, protected from light, and stored at room temperature, the solution was stable for up to 96 hours [22].

1 mg/mL furosemide with 10 mg/mL chlorothiazide solution: When combined together in a polypropylene syringe, protected from light, and stored at room temperature, the solution was stable for up to 96 hours [22].

- Reconstitute chlorothiazide 500 mg (18 mL of bacteriostatic water for injection for a final concentration of 28 mg/mL)
- Add 3.57 mL of chlorothiazide 28 mg/mL solution to 1 mL of furosemide 10 mg/mL solution
- Add D_5W for a final volume of 10 mL.

Ganciclovir

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

6 mg/kg/dose IV every 12 hours. Treat for a minimum of 6 weeks if possible. Reduce the dose by half for significant neutropenia (less than 500 cells/mm^3).

Chronic Oral Suppression: 30 to 40 mg/kg/dose orally every 8 hours.

HIV Infection - Congenital Cytomegalovirus (CMV) Infection: 6 mg/kg IV every 12 hours for 6 weeks [1]

Uses

Prevention of progressive hearing loss and lessening of developmental delays in babies with symptomatic congenital cytomegalovirus infection involving the central nervous system.

Cytomegalovirus (CMV) - HIV Infection: Ganciclovir is recommended as a first-line agent for congenital CMV infection in patients with HIV co-infection [1].

Administration

Use proper procedures for handling and disposal of chemotherapy; drug is potentially carcinogenic and mutagenic.

Intravenous: Infuse over a period of 1 hour in compatible solution at a concentration not to exceed 10 mg/mL. Phlebitis and/or pain may occur at intravenous infusion site; infuse preferably via plastic cannula into veins with adequate blood flow, permitting rapid dilution and distribution [2].

Do not administer by IM or subQ routes as severe tissue irritation may occur [3].
Use proper procedures for handling and disposal of chemotherapy, drug is potentially carcinogenic and mutagenic [3].
Avoid direct contact of the skin or mucous membranes with the IV solution. If contact occurs, wash thoroughly with soap and water; rinse eyes thoroughly with plain water [3].
In the preparation and administration of injections, the National Institute for Occupational Safety and Health (NIOSH) recommends the use of double gloves and a protective gown. Prepare in a biological safety cabinet or a compounding aseptic containment isolator; eye/face and respiratory protection may be needed. Prepare compounds in a closed system

drug transfer device. During administration, if there is a potential that the substance could splash or if the patient may resist, use eye/face protection. Administer certain dosage forms via a closed system drug transfer device [4].

MEDICATION SAFETY

Contraindications/Precautions

Precautions
Hematologic: Use not recommended if absolute neutrophil count less than 500 cells/mcL, hemoglobin less than 8 g/dL, or platelet count less than 25,000 cells/mcL [2].
Hematologic: Use caution in patients with cytopenias or in patients receiving myelosuppressive drugs or irradiation; monitoring recommended [2].
Renal: Use caution in patients with impaired renal function; monitoring and possible dosage reduction recommended [2].

Adverse Effects

Significant neutropenia will occur in the majority of treated patients. Discontinue treatment if the neutropenia does not resolve after reducing the dosage by half.

Black Box Warning

Warning: Hematologic Toxicity, Impairment of Fertility, Fetal Toxicity, Mutagenesis and Carcinogenesis[2]

- **Hematologic Toxicity:** Granulocytopenia, anemia, thrombocytopenia, and pancytopenia have been reported in patients treated with ganciclovir sodium.
- **Impairment of Fertility:** Based on animal data and limited human data, ganciclovir sodium may cause temporary or permanent inhibition of spermatogenesis in males and suppression of fertility in females.
- **Fetal Toxicity:** Based on animal data, ganciclovir sodium has the potential to cause birth defects in humans
- **Mutagenesis and Carcinogenesis:** Based on animal data, ganciclovir sodium has the potential to cause cancers in humans

Solution Compatibility

NS, D_5W, and LR.

Terminal Injection Site Compatibility

Enalaprilat, fluconazole, linezolid, propofol, and remifentanil.

Terminal Injection Site Incompatibility

Fat emulsion. Aztreonam, cefepime, and piperacillin/tazobactam.

Monitoring

CBC every 2 to 3 days during first 3 weeks of therapy, weekly thereafter if stable.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Ganciclovir is an acyclic nucleoside analog of guanine that inhibits replication of herpes viruses in vivo. There is large interpatient variability in pharmacokinetic parameters. Mean half-life in infants less than 49 days postnatal age is 2.4 hours. Metabolism is minimal; almost all drug is excreted unchanged in the urine via glomerular filtration and active tubular secretion.

ABOUT

Special Considerations/Preparation

Injection

Cytovene® is supplied as lyophilized powder for injection, 500 mg per vial. Reconstitute by injecting 10 mL of sterile water for injection into the vial. Do not use bacteriostatic water for injection containing parabens; it is incompatible with ganciclovir and may cause precipitation. Shake the vial to dissolve the drug. Visually inspect the reconstituted solution for particulate matter and discoloration prior to proceeding with infusion solution. Discard the vial if particulate matter or discoloration is observed.

Reconstituted solution in the vial is stable at room temperature for 12 hours. **Do not refrigerate,** may cause precipitation. The pH is approximately 11; use caution when handling. Osmolarity is 320 mOsm/kg [5].

Based on patient weight, remove the appropriate volume of the reconstituted solution (ganciclovir concentration 50 mg/mL) from the vial and add to a compatible diluent fluid to make a final infusion concentration less than 10 mg/mL. Although stable for 14 days, the infusion solution must be used within 24 hours of dilution to reduce the risk of bacterial contamination. Refrigerate the infusion solution. **Do not freeze**[5].

Oral

Available as 250-mg and 500-mg capsules. *The marketing and distribution of ganciclovir capsules and intravitreal implants have been discontinued. This decision is not related to product safety or efficacy.*

Extemporaneous Oral Suspension

Oral suspension (25 mg/mL): A 25 milligrams/milliliter ganciclovir oral suspension was prepared with ganciclovir intravenous formulation. Reconstitute 5-500 milligram vials (3 milliliters in each vial) of ganciclovir injection with sterile water. Withdraw total volume (15 milliliters) and transfer to an amber bottle. Add 50 milliliters of Orasweet and shake well. Add 1 milliliter of 3% hydrogen peroxide and shake well. Add a sufficient quantity of Orasweet for a final volume of 100 milliliters. The suspension is stable for 28 days at room temperature [6].

Oral suspension (100 mg/mL): Prepare oral suspension in a vertical-flow laminar hood. Oral suspension (100 mg/mL) may be prepared by emptying eighty (80) 250-mg capsules into a glass mortar wetted and triturated with choice of vehicle (Oral-Sweet OR Ora-Sweet SF) to a smooth paste. Add 50-mL of vehicle to the paste, mix, and transfer contents to an amber polyethylene terephthalate bottle. Rinse the mortar with another 50 mL of vehicle and transfer contents to the bottle. Add enough vehicle to make a final volume of 200 mL. Stable for 123 days when stored at 23 to 25 degrees C. **Protect from light**[7].

The National Institute for Occupational Safety and Health (NIOSH) recommends the use of double gloves and a protective gown by anyone compounding a hazardous oral liquid or preparing any hazardous drug for administration by feeding tube. If possible, prepare in a control device. Respiratory, eye, and face protection are needed if not done in a control device [4].

Gentamicin

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

KIDs List: Avoid use of gentamicin ophthalmic ointment in neonates due to risk of severe ocular reactions [3].

Extended-Interval Dosing

Preterm and Term: 5 mg/kg/dose IV every 36 hours achieved a mean Cmax of 9.2 mg/L and Cmin of 0.7 mg/L in neonates 34 weeks' or less gestation (n=25) and 10.9 mg/L and 0.47 mg/L, respectively, in neonates greater than 35 weeks' gestation (n=23) [4][5].

Standard Dosing:

Renal function and drug elimination are most strongly correlated with Postmenstrual Age (PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.

Dosing Chart			
PMA (weeks)	**Postnatal (days)**	**Dose (mg/kg)**	**Interval (hours)**
≤29*	0 to 7 8 to 28 ≥29	5 4 4	48 36 24
30 to 34	0 to 7 ≥8	4.5 4	36 24
≥35	ALL	4	24
* or significant asphyxia, PDA, or treatment with indomethacin			

In neonates younger than 7 days dosed according to the above standard dosing regimen, initial peak and trough concentrations were predicted to be 6 to 10 mg/L and less than 1 mg/L, respectively, based on population pharmacokinetic parameters (n=177 neonates) [1]. The above standard dosing regimen attained trough concentrations of 1 mg/L or less and 0.5 mg/L or less in 50% and 17%, respectively, of dose simulations (n=5,000). Likewise, peak concentrations of 5 to 12 mg/L, greater than 12 mg/mL, and less than 5 mg/L were attained in 75%, 20%, and 6%, respectively, of dose simulations [2].

Dosage Adjustment

Hypothermia: Small retrospective pharmacokinetic studies demonstrated reduced clearance in neonates during hypothermia for hypoxic-ischemic encephalopathy suggesting a need for increased dosing intervals and close target drug monitoring [6][7][8][9]. Prospective clinical trials to evaluate dose regimens are needed [7].

Uses

Treatment of infections caused by aerobic gram-negative bacilli (eg, *Pseudomonas, Klebsiella, E coli*). Usually used in combination with a β-lactam antibiotic.

Infective endocarditis: The following recommendations are based on a consensus of experts [12]. The full pediatric guidelines can be found here: https://doi.org/10.1161/CIR.0000000000000298

<table>
<tr><th colspan="3">Initial Empirical Therapy or Culture-Negative Endocarditis*</th></tr>
<tr><td>Unknown Organism</td><td>First-Choice</td><td>Alternative Choice</td></tr>
<tr><td>Native valve (community acquired)</td><td rowspan="2">Ampicillin/sulbactam + gentamicin with or without vancomycin
For prosthetic valve involvement, add rifAMPin</td><td rowspan="2">Vancomycin + gentamicin</td></tr>
<tr><td>"Late" prosthetic valve infection (more than 1 year after surgery)</td></tr>
<tr><td>Nosocomial endocarditis associated with vascular cannulae</td><td rowspan="2">Vancomycin + gentamicin (with or without rifAMPin if prosthetic material present) + cefepime or cefTAZidime</td><td rowspan="2">Unknown</td></tr>
<tr><td>"Early" prosthetic valve endocarditis (1 year or less after surgery)</td></tr>
<tr><td colspan="3">* Culture-negative endocarditis (CNE): generally, attempt to culture the infecting organism for at least 48 hours. Severely ill children need immediate treatment. Consider infectious disease consultation for CNE</td></tr>
<tr><td colspan="3">Baltimore, 2015</td></tr>
</table>

<table>
<tr><th colspan="3">Organism Directed Therapy</th></tr>
<tr><td>Organism</td><td>First-Choice</td><td>Alternative Choice</td></tr>
<tr><td>Streptococci</td><td colspan="2"></td></tr>
<tr><td>Highly susceptible to penicillin G (MBC 0.1 mcg/mL or less); includes most viridans streptococci, groups A, B, C, G</td><td>Penicillin G or CefTRIAXone</td><td>Vancomycin or First-generation cephalosporin or CefTRIAXone</td></tr>
</table>

nonenterococcal, group D streptococci (S bovis, S equinus)		
Relatively resistant to penicillin (MBC 0.2 mcg/mL or more); less-susceptible viridans streptococci or enterococci	Penicillin G or Ampicillin + Gentamicin (for first 2 weeks, or entire course for enterococci)	Vancomycin + Gentamicin for enterococci Ampicillin + CefTRIAXone (for aminoglycoside (AMG)-resistant enterococci or AMG-intolerant patient) CefTRIAXone + gentamicin (not for enterococcal endocarditis)
Resistant to penicillin	Consult an infectious disease specialist.	---
Staphylococci (S aureus or coagulase-negative staphylococci) †		
Penicillin G susceptible (1 mcg/mL or less) (rare)	Penicillin G	Oxacillin or Nafcillin or First-generation cephalosporin or Vancomycin
Penicillin G resistant (0.1 mcg/mL)	Oxacillin or Nafcillin with or without Gentamicin	Vancomycin (for those highly allergic to beta-lactam antibiotics) or First-generation cephalosporin
Oxacillin (MRSA) resistant (4 mcg/mL)	Vancomycin	Daptomycin for right-sided endocarditis, maybe for left-sided
Vancomycin resistant or intolerant	Daptomycin	Unknown
	†When prosthetic material present add riFAMpin +	

	gentamicin (for first 2 weeks) for all staphylococci	
Gram-negative enteric bacilli	CefTAZidime or Cefepime or Cefotaxime or CefTRIAXone Plus gentamicin (or tobramycin or amikacin, depending on susceptibility)	Broad-spectrum penicillin Plus gentamicin (or tobramycin or amikacin)
HACEK group	CefTRIAXone or Cefotaxime or Ampicillin-sulbactam	Ampicillin (when susceptible) Plus aminoglycoside
KEY: AMG = aminoglycosides; HACEK = Haemophilus species, Aggregatibacter species, Cardiobacterium hominis, Eikenella corrodens, and Kingella species; MBC = minimum bactericidal concentration, MRSA = methicillin-resistant Staphylococcus aureus (includes resistance to oxacillin, nafcillin, and cephalosporins)		
Baltimore, 2015		

Meningitis: Empiric agents for the treatment of meningitis in neonates are ampicillin, gentamicin, and cefotaxime [13]. Reassess therapy based on culture and sensitivity results [14].

Sepsis

Ampicillin plus gentamicin are the agents of choice for empirical treatment of early-onset sepsis (EOS) in neonates at most risk for EOS. Broad-spectrum antibiotics may be necessary in neonates who are severely ill, particularly preterm neonates at high risk for EOS after prolonged antepartum maternal antibiotic treatment [15][16].

Gestational age 34 6/7 weeks or younger

Highest Risk for EOS: Administer empirical antibiotics in those at highest risk; neonates born preterm because of maternal cervical incompetence, preterm labor, premature rupture of membranes, clinical concern for intraamniotic infection, or acute onset of unexplained nonreassuring fetal status [15]

Low Risk: Consider empirical antibiotics based on the risks and benefits. Those at low risk are those born preterm by cesarean delivery because of maternal noninfectious illness or placental insufficiency in the absence of labor, attempts to induce labor, or rupture of membranes before delivery [15]

Gestational age 35 0/7 weeks or older: Administer empirical antibiotics based on level of risk. Multiple approaches of determining risk may be used including categorical algorithms, multivariate risk assessments, or serial physical examinations [16]

Duration:

•Discontinue antibiotics by 36 to 48 hours when blood cultures are sterile, unless a site-specific infection has been identified, for preterm and full term neonates [15][16].

•Procalcitonin values in addition to perinatal risk factors, signs and symptoms, and laboratory values may aid in the determination to discontinue antibiotic therapy in neonates with suspected early-onset sepsis. The duration of antibiotic therapy was reduced by 9.9 hours with a procalcitonin-guided algorithm compared with standard care in a multicenter randomized controlled trial of 1710 neonates born after 34 weeks of gestational age with possible or unlikely sepsis. Re-infection and mortality was not different between the groups (risk difference 0.1% (95% CI, -5.2% to 5.3%) [17].

Administration

Infuse over a period of 30 to 120 minutes using a concentration of 2 mg/mL or 10 mg/mL [10][11] .

Administer as a separate infusion from penicillin-containing compounds. IM injection is associated with variable absorption, especially in the very small infant.

MEDICATION SAFETY

Adverse Effects

Transient and reversible renal tubular dysfunction may occur, resulting in increased urinary losses of sodium, calcium, and magnesium. Vestibular and auditory ototoxicity may occur. The addition of other nephrotoxic and/or ototoxic medications (eg, furosemide, vancomycin) may increase these adverse effects. Increased neuromuscular blockade (ie, neuromuscular weakness and respiratory failure) may occur when used with pancuronium or other neuromuscular blocking agents and in patients with hypermagnesemia. The use of gentamicin ointment for newborn ocular prophylaxis has been associated with periocular ulcerative dermatitis.

Black Box Warning

Aminoglycoside therapy has been associated with potential neurotoxicity, ototoxicity, and nephrotoxicity. Patients with impaired renal function, dehydration, and those who receive high dosage or prolonged therapy are at an increased risk of toxicity. Discontinue therapy or adjust dose if there is evidence of ototoxicity or nephrotoxicity. Aminoglycoside ototoxicity is usually irreversible.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Acyclovir, alprostadil, amiodarone, aztreonam, caffeine citrate, cefepime, cefotaxime, cefoxitin, ceftazidime, ceftriaxone, cimetidine, clindamycin, dopamine, enalaprilat, esmolol, famotidine, fluconazole, gentamicin, heparin (concentrations of 1 unit/mL or less), insulin, linezolid, lorazepam, magnesium sulfate, meropenem, metronidazole, midazolam, milrinone, morphine, nicardipine, pancuronium bromide, penicillin g, prostaglandin E_1, ranitidine, remifentanil, vecuronium, and zidovudine.

Terminal Injection Site Incompatibility

Amphotericin B, ampicillin, azithromycin, furosemide, imipenem/cilastatin, heparin (concentrations greater than 1 unit/mL), indomethacin, mezlocillin, nafcillin, oxacillin, propofol, and ticarcillin/clavulanate.

Monitoring

Measure serum concentrations when treating for more than 48 hours. Obtain peak concentration 30 minutes after end of infusion, and trough concentration just prior to the next dose [18]. When treating patients with serious infections or significantly changing fluid or renal status consider measuring the serum concentration at 22- or 24-hours after a dose, and use the tables below for the suggested dosing interval. Blood samples obtained to monitor serum drug concentrations should be spun and refrigerated or frozen as soon as possible.
Routine measurement of gentamicin concentrations are probably not necessary in full-term neonates without risk factors (low urine output, evidence of renal impairment, presence of shock, and/or concomitant use of nephrotoxic drugs) [19][20].

Therapeutic Serum Concentration
Peak: 5 mg/L or more [21][22][23][24]; (8 to 13 mg/L for extended-interval dosing) [4]
Trough: 2 mg/L or less [4][21][23][22][24]; less than 1 mg/L is also suggested [21][22][23].

Serum concentrations measured 22 hours post-first-dose may be used to determine dosing intervals in neonates [21][22]:

22-Hour Post-First Dose (5 mg/kg)	
Concentration at 22 hours (mg/L)*	**Suggested Dosing Interval (hours)****

≤ 1.2	24
1.3 to 2.6	36
2.7 to 3.5	48
≥ 3.6	Hold dose Measure concentration in 24 hours
*Studies did not include infants with urine output less than 1 mL/kg/hr, hypoxic ischemic encephalopathy, or coadministration of indomethacin. **A mean peak concentration of 10.55 mg/L (range, 6.8 to 15.1 mg/L) and a mean trough concentration of 0.75 mg/L (range, less than 0.4 to 1.7 mg/L) in infants 1 week or younger (23 weeks gestation to term; n=104) and 9.8 mg/mL and 0.6 mg/mL, respectively, in infants older than 7 days (24 weeks gestation to 36 weeks; n=38) were achieved with 5 mg/kg/dose at the suggested frequency.	
Dersch-Mills, 2016; Dersch-Mills, 2012	

Serum concentrations measured 24 hours post-dose may be used to determine dosing intervals in neonates:

24- hour Concentration Suggested Dosing Intervals		
Concentration at 24 hours (mg/L)	**Half-life (hours)**	**Suggested Dosing Interval (hours)**
≤1	~ 8	24
1.1 to 2.3	~ 12	36
2.4 to 3.2	~ 15	48
≥3.3	--	Measure level in 24 hours

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Dosing recommendations are based on: (1) Higher peak concentrations increase concentration-dependent bacterial killing; (2) There is a post-antibiotic effect on bacterial killing, especially when treating concurrently with a β-lactam antibiotic; (3) There may be less toxicity with less frequent dosing, due to less renal drug accumulation. Volume of distribution is increased and clearance is decreased in patients with PDA. Serum half-life is

prolonged in premature and asphyxiated newborns. Inactivation of gentamicin by penicillin-containing compounds appears to be a time-, temperature-, and concentration-dependent process. This is probably clinically significant only when penicillin-containing compounds are mixed in IV solutions or when the blood is at room temperature for several hours before the assay is performed.

Pharmacokinetic Parameters

Volume of Distribution: The table below provides the Vd in neonates [4][21][22]:

Volume of Distribution					
Postnatal age	Gestational Age				Author
	28 weeks or less	29 to 32 weeks	33 to 36 weeks	37 weeks or more	
Older than 1 week	0.55 L/kg	0.56 L/kg	0.55 L/kg	0.55 L/kg	Dersch-Mills, 2016 (n=40)
1 week or younger	0.6 L/kg	0.5 L/kg	0.5 L/kg	0.5 L/kg	Dersch-Mills, 2012 (n=104)
1 to 32 days (mean 6 days)	34 weeks or less				El-Chaar, 2016 (n=48)
	0.6 L/kg				
1 to 3 days (mean 1.4 days)	More than 34 weeks				
	0.48 L/kg				

Clearance: In neonates 1 to 32 days of age (mean 6 days; 34 weeks or less gestation), the clearance was 0.06 L/hr/kg. In neonates 1 to 3 days of age (mean 1.4 days; more than 34 weeks gestation), the clearance was 0.14 L/hr/kg [4].

Half-life: The table below provides the half-lives in neonates [4][21][22]:

Half-lives					
Postnatal age	Gestational Age				Author
	28 weeks or less	29 to 32 weeks	33 to 36 weeks	37 weeks or more	
Older than 1 week	10.2 hours	6.5 hours	5.9 hours	5 hours	Dersch-Mills, 2016 (n=40)

1 week or younger	11.2 hours	10.8 hours	8.7 hours	7.6 hours	Dersch-Mills, 2012 (n=104)
1 to 32 days (mean 6 days)	34 weeks or less				
	9.8 hours				El-Chaar, 2016 (n=48)
1 to 3 days (mean 1.4 days)	More than 34 weeks				
	7.7 hours				

Controlled Hypothermia
Dosage: Doses of 5 mg/kg every 36 hours for neonates with gestational ages (GA) of 36 to 40 weeks and 5 mg/kg every 24 hours for neonates of GA 42 weeks, undergoing hypothermia within 6 hours after birth, were recommended based on dose simulations (n=5,000) from a multicenter prospective observational cohort study (n=47). Targets were less than 1 mg/L for trough and 8 to 10 mg/L for peak gentamicin concentrations [6].
Clearance: Clearance of gentamicin was unchanged during days 1 to 3 of hypothermia and day 4 of rewarming and 29% higher on day 5 of normothermia compared with preceding phases in a multicenter prospective observational cohort study of 47 neonates more than 37 weeks gestational age (GA). Clearance was 1.89 L/hr/70 kg (0.027 L/hr/kg) during hypothermia phase [6].
Vd: During hypothermia, Vd was unchanged. Vd from the central and peripheral compartments were 32.5 L/70 kg (0.46 L/kg) and 30.3 L/70 kg (0.43 L/kg), respectively [6].

ABOUT

Special Considerations/Preparation

Pediatric injectable solution available in a concentration of 10 mg/mL.

Glucagon

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Hypoglycemia, Refractory
200 mcg/kg/dose (0.2 mg/kg/dose) IV push, IM, or subQ.
Maximum dose: 1 mg.
Continuous infusion: Begin with 10 to 20 mcg/kg/hour; doses of 0.5 to 1 mg per day regardless of age or weight have been used, given as a continuous infusion [1][2]. Rise in blood glucose should occur within one hour of starting infusion [1].

Uses

Treatment of hypoglycemia refractory to intravenous dextrose infusions, or when dextrose infusion is unavailable, or in cases of documented glucagon deficiency.

Administration

• May administer subQ, IM, or IV (under medical supervision) [3][4].
The reconstituted solution is 1 mg/mL[3][4].
Immediately after reconstitution, inject solution subcutaneously or intramuscularly in the upper arm, thigh, or buttocks, or intravenously [3][4].
• When patient has responded to treatment and is able to swallow, give oral carbohydrates [3][4].
• Discard any unused portion [3][4].
For continuous infusion, glucagon in 10% dextrose has been used [2]. There are no stability or concentration data available for glucagon in 10% dextrose.

MEDICATION SAFETY

Contraindications/Precautions

Contraindications[3]
- Pheochromocytoma
- Insulinoma

- Glucagonoma when used as a diagnostic aid

Precautions
Concomitant use: Use with anticholinergic drugs is not recommended [3].
Cardiovascular: If a substantial increase in blood pressure occurs and a previously undiagnosed pheochromocytoma is suspected, treatment is required [3]
Cardiovascular: Increased myocardial oxygen demand, blood pressure, and pulse rate may occur and be life-threatening in patients with cardiac disease; monitoring recommended in patients with cardiac disease during use of glucagon as a diagnostic aid [3]
Dermatologic: Necrolytic migratory erythema has been reported with continuous glucagon infusion; discontinuation may be necessary. Consider risks versus benefits of continuous infusion therapy if necrolytic migratory erythema occurs [3]
Endocrine and metabolic: Increase in blood glucose may occur initially in patients with insulinoma, however, exaggerated insulin release may also occur; treat symptoms of hypoglycemia with oral or IV glucose [3].
Endocrine and metabolic: Inadequate reversal of hypoglycemia due to low levels of releasable glucose in the liver may occur in patients with adrenal insufficiency, chronic hypoglycemia, prolonged fasting, or starvation; patients with these conditions should be treated with glucose [3].
Endocrine and metabolic: May cause hyperglycemia in patients with diabetes mellitus; monitoring recommended [3]
Endocrine and metabolic: Secondary hypoglycemia may occur in patients with glucagonoma; test patients suspected of having glucagonoma for blood levels of glucagon prior to use as a diagnostic aid [3].
Immunologic: Allergic reactions (eg, generalized rash, hypotension, or anaphylactic shock with breathing difficulties) have been reported [3].

Adverse Effects

Nausea and vomiting, tachycardia, and ileus. Hyponatremia and thrombocytopenia have also been reported.

Monitoring

Follow blood glucose concentration closely. Watch for rebound hypoglycemia. Rise in blood glucose will last approximately 2 hours.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action: Glucagon for injection is a polypeptide hormone identical to human glucagon that increases blood glucose and relaxes smooth muscle of the gastrointestinal tract. Stimulates gluconeogenesis (acts only on liver glycogen, converting it to glucose) [5].

ABOUT

Special Considerations/Preparation

Injection route (GlucaGen®)
Availability: 1-mg single-dose vials [3].
Preparation
• Using the supplied prefilled syringe, insert the needle through the rubber stopper of the vial containing glucagon powder and inject all of the liquid from the syringe into the vial [3].
• Gently shake the vial until the powder is completely dissolved and no particles remain in the fluid [3].
• Visually inspect for particulate matter and discoloration. If the solution is cloudy or contains particulate matter, do not use [3].
• Use immediately after reconstitution. Discard any unused portion [3].
The reconstituted solution is 1 mg/mL[3].

Intranasal route (Baqsimi™)
Availability: 3-mg intranasal device of glucagon [6].
Storage: Store in provided shrink-wrapped tube at temperatures up to 30 degrees C (86 degrees F). Keep in shrink-wrapped tube until ready for use. An opened tube exposed to moisture may not work as expected. Discard after use as each device contains 1 dose of drug and cannot be reused [6].

SubQ route (Gvoke™)
Availability: 0.5 mg/0.1 mL and 1 mg/0.2 mL single dose prefilled HypoPen autoinjector; 0.5 mg/0.1 mL and 1 mg/0.2 mL single-dose prefilled syringe [7]
Storage: Store at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F). Store in original sealed foil pouch until time of use. Do not expose to extreme temperatures. Discard after use as each device contains a single dose of drug and cannot be reused [7]

Heparin

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Extracorporeal membrane oxygenation (ECMO); anticoagulation
Loading dose, before ECMO cannulation: 100 units/kg IV loading dose before ECMO cannulation. In patients who cannot be weaned from cardiopulmonary bypass (CPB), consider forgoing the loading dose of heparin to reduce the risk of bleeding as the patient should already be adequately anticoagulated [1]
Continuous infusion: Maintain a continuous IV infusion to target the activated clotting time (ACT) between 180 and 220 seconds [1]

Maintaining patency of central vascular catheters:
0.5 units/kg/hour [2][3].

Maintaining patency of peripheral vascular catheters:
0.5 to 1 unit/mL of IV fluid.

Treatment of thrombosis: 75 units/kg IV over 10 minutes, followed by 28 units/kg per hour continuous infusion. Four hours after initiating therapy, measure aPTT, then adjust dose to achieve an aPTT that corresponds to an anti-factor X_a level of 0.35 to 0.7 (this is usually equivalent to an aPTT of 60 to 85 seconds). Treatment should be limited to 10 to 14 days. Some experts recommend switching to low molecular weight heparin after 3 to 5 days. For renal vein thrombosis requiring treatment, 6 weeks to 3 months of heparin/low molecular weight heparin therapy is recommended [2].

Uses

Extracorporeal membrane oxygenation (ECMO), anticoagulation: The American Heart Associated (AHA) recommends a loading dose of heparin before ECMO cannulation in pediatric patients. A continuous infusion should be maintained to target an activated clotting time (ACT) between 180 to 220 seconds. In patients who cannot be weaned from cardiopulmonary bypass (CPB), consider forgoing the loading dose of heparin to reduce the risk of bleeding as the patient should already be adequately anticoagulated [1]

Maintenance of peripheral arterial and central venous catheter patency. Only continuous infusions (rather than intermittent flushes) have been demonstrated to maintain catheter patency. Treatment of thrombosis. Unilateral renal vein thrombosis (without renal impairment or extension to inferior vena cava) may be managed with supportive care and radiologic monitoring or heparin/low molecular weight heparin. Bilateral renal vein thromboses should be managed with heparin/low molecular weight heparin [2]. Although data are limited, enoxaparin may be preferable to heparin for treatment of thromboses.

Call 1-800-NOCLOTS for case reporting and treatment guidance.

Administration

Intravenous: Administer IV loading doses over 10 minutes. Administer maintenance infusion by continuous IV infusion in compatible solution (various concentrations may be used) [2]. The concentrations are typically from 100 units/mL to 500 units/mL for loading doses and 10 to 500 units/mL for continuous IV infusion.
Make certain correct concentration is used.
Avoid intramuscular administration due to possibility of hematoma formation[4].

Effective October 1, 2009, a revised United States Pharmacopeia (USP) reference standard and test method has resulted in an approximately 10% reduction in heparin potency per USP unit. It is unlikely that the change in potency will have clinical significance. Clinicians should be aware of this change in potency in the event that there are any differences in response to heparin therapy in practice. Manufacturers will provide an identifier (an 'N' next to the lot number) on heparin products made under the new USP standards [5][6].

MEDICATION SAFETY

Contraindications/Precautions

Contraindicated in infants with evidence of intracranial or GI bleeding or thrombocytopenia (below 50,000/mm^3). Data are insufficient to make specific recommendations regarding anticoagulation therapy. Heparin-induced thrombocytopenia (HIT) has been reported to occur in approximately 1% of newborns exposed to heparin. Heparin-associated antiplatelet antibodies were found in half of the newborns who were both thrombocytopenic and heparin-exposed. Although the thrombocytopenia resolved spontaneously in most patients upon stopping the heparin, a high incidence of ultrasonographic-documented aortic thrombosis was seen. Long term use of therapeutic doses of heparin can lead to osteoporosis.
Confirm heparin vial concentration prior to administration of the drug. Fatal hemorrhages have occurred in pediatric patients when the incorrect heparin concentration was administered.

Solution Compatibility

D_5W, $D_{10}W$, NS, and ½ NS.

Terminal Injection Site Compatibility

Acyclovir, aminophylline, amphotericin B, ampicillin, atropine, aztreonam, caffeine citrate, calcium gluconate, cefazolin, cefepime, cefotaxime, cefoxitin, ceftazidime, ceftriaxone, chloramphenicol, cimetidine, clindamycin, dexamethasone, digoxin, dobutamine, dopamine, enalaprilat, epinephrine, erythromycin lactobionate, esmolol, famotidine, fentanyl, fluconazole, flumazenil, furosemide, micafungin, hydralazine, hydrocortisone succinate, ibuprofen lysine, insulin, isoproterenol, lidocaine, linezolid, lorazepam, meropenem, metoclopramide, metronidazole, midazolam, milrinone, morphine, nafcillin, naloxone, neostigmine, nitroglycerin, oxacillin, pancuronium bromide, penicillin G, phenobarbital, phytonadione, piperacillin, piperacillin/tazobactam, potassium chloride, procainamide, propofol, propranolol, ranitidine, remifentanil, sodium bicarbonate, sodium nitroprusside, ticarcillin/clavulanate, trimethoprim/sulfamethoxazole, vecuronium, and zidovudine.

Terminal Injection Site Incompatibility

Alteplase, amikacin, amiodarone, caspofungin, diazepam, gentamicin, hyaluronidase, methadone, netilmicin, phenytoin, tobramycin, and vancomycin.

Monitoring

Follow platelet counts every 2 to 3 days. When treating thromboses, maintain a prolonged aPTT in a range corresponding to an anti-factor X_a level of 0.3 to 0.7 units/mL (usually equivalent to an aPTT of 60 to 85 seconds). Assess for signs of bleeding and thrombosis.

Extracorporeal membrane oxygenation (ECMO), anticoagulation
Therapeutic and Toxic Laboratory Monitoring
Monitor activated clotting time (ACT) at least every hour during extracorporeal support (target ACT, 180 to 220 seconds) [1]
Monitor anti-FXa levels, PT, PTT, fibrinogen, platelet count, and AT III levels at least daily. In particular, the PTT (target, 1.5 to 2.5 times control) and anti-FXa levels (target, 0.3 to 0.7 units/mL) should be repeated as necessary to confirm adequate anticoagulation [1]

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Activates antithrombin III, which progressively inactivates both thrombin and factor X_a, key proteolytic enzymes in the formation of fibrinogen and activation of prothrombin. Efficacy in neonates is decreased due to low antithrombin plasma concentrations. Metabolized by liver.

Renal excretion should occur within 6 hours, but may be delayed. Clearance in neonates is more rapid than in children or adults. Half-life is dose-dependent, but averages 1 to 3 hours.

ABOUT

Special Considerations/Preparation

Keep protamine sulfate on hand to manage hemorrhage (see Protamine monograph for appropriate dosing).

Heparin available in 10 units/mL (for IV reservoirs); 100 units/mL; 1000 units/mL (for central catheters); 5000 units/mL, 10,000 units/mL, and 20,000 units/mL. Also available in premixed infusion bags in D_5W, NS, and ½ NS in various concentrations.

Hepatitis B Immune Globulin (Human)

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Prevention of Perinatal HBV Transmission
Dosage: 0.5 mL IM plus first hepatitis B vaccine dose; may administer at the same time but at different anatomical sites [1][2][3][4]. If hepatitis B vaccination is delayed by as long as 3 months, give a second 0.5-mL dose at 3 months. If vaccination is refused, give a second 0.5-mL dose at 3 months and a third dose at 6 months [2]
Patient selection and timing:
• **HBsAg-positive mother, any birth weight:** Administer within 12 hours of birth [1]
• **HBsAg-unknown mother, birth weight less than 2000 g:** Administer within 12 hours of birth [1]
• **HBsAg-unknown mother, birth weight 2000 g or greater:** Administer only if mother is found to be positive; give as soon as possible once results are known but no later than 7 days of age [1]

Uses

Passive immunization of newborns whose mothers have acute hepatitis B infection at the time of delivery, or who are HBsAg-positive. Infants born to mothers who are HBeAg-positive have the highest risk.

Administration

For infants, the recommended site of administration is the anterolateral thigh. A 22- to 25-gauge needle should be used, and the appropriate needle length is 7/8 inch to 1 inch [5].

When given at the same time as the first dose of hepatitis B vaccine, use a separate syringe and a different site. Care should be taken to draw back on the plunger of the syringe before injection to be certain the needle is not in a blood vessel [3][4].

MEDICATION SAFETY

Adverse Effects

Local pain and tenderness may occur at the injection site.
Do not administer IV because of the risk of serious systemic reactions. Serious complications of IM injections are rare. Universal precautions should be used with neonates born to HBsAg-positive mothers until they have been bathed carefully to remove maternal blood and secretions.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Hepatitis B Immune Globulin (human) is a hyperimmune globulin solution prepared from pooled plasma of individuals with high titers of antibody to hepatitis B surface antigen (anti-HBsAg). All donors are HBsAg-negative and HIV-antibody negative. Nabi-HB® (Nabi) is a solvent detergent treated and thimerosal free hepatitis B immune globulin preparation [3][4].

ABOUT

Special Considerations/Preparation

Potency: Nabi-HB® and HepaGam® have an approximate potency of greater than 312 international units/mL [3][4]. HyperHEP B® has an approximate potency of 220 international units/mL [2]
Availability: Nabi-HB® and HepaGam® are available in a 1-mL or 5-mL single-dose vial. HyperHEP B® is available as a 0.5-mL neonatal single-dose syringe, a 1-mL single-dose syringe, and as a 1-mL or 5-mL single-dose vial [2].
Storage: Refrigerate between 2 to 8 degrees C (36 to 46 degrees F) [2][3][4]. Use Nabi-HB® and HepaGam® within 6 hours after vial has been entered [3][4].

Hepatitis B Vaccine (Recombinant)

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Engerix-B® 10 mcg (0.5 mL) or Recombivax HB® 5 mcg (0.5 mL) IM [1][2].

Birth Dose
Maternal HBsAg-Positive: Administer first dose before 12 hours of age regardless of birth weight. Administer in combination with 0.5 mL of hepatitis B immune globulin. For infants less than 2000 g, administer 3 additional doses of vaccine (4 total) starting at 1 month of age. These infants should be tested for HBsAg and HBsAg antibodies at 9 to 12 months of age or 1 to 2 months after completion of the hepatitis B vaccine series if the series was delayed [3].
Maternal HBsAg Unknown: Administer first dose before 12 hours of age. If birthweight less than 2000 g, administer in combination with 0.5 mL hepatitis B immune globulin within 12 hours of birth. Administer 3 additional doses of vaccine (4 total) starting at 1 month of age. If birthweight 2000 g or greater and mother subsequently tests HBsAg positive, administer hepatitis B immune globulin to infant within 7 days of birth [3].

Maternal HBsAg Negative: Administer first dose within 24 hours of birth for medically stable infants 2000 g or more. Infants less than 2000 g, administer 1 dose at chronological age 1 month or hospital discharge (whichever is earlier, and even if weight is still less than 2000 g) [3].

After Birth Doses:
• Administer 2nd dose at 1 to 2 months of age and 3rd dose at 6 to 18 months of age; use monovalent HepB vaccine if doses are administered before 6 weeks of age [3]
• If a birth dose was not received, begin 3-dose series (give at intervals of 0, 1 to 2 months, and 6 months) as soon as possible [3]
• A minimum interval of 4 weeks is recommended between dose 1 and 2 [3]
• Administer dose 3 at least 8 weeks after dose 2 and at least 16 weeks after dose 1 (when 4 doses are given, substitute "dose 4" for "dose 3" in these calculations) [3]
• A total of 4 doses of HepB vaccine is acceptable if a combination vaccine that contains HepB is administered after the birth dose [3]
• Do not administer the final dose (third or fourth) earlier than 24 weeks of age [3]

Catch-up Schedule: Complete a 3-dose series (give at intervals of 0, 1 to 2 months, and 6 months) for any unvaccinated patient [3]

Uses

Complete immunization schedules and guidance can be found at the following link:

https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html

Immunoprophylaxis against hepatitis B [1][2]. Premature infants who have received the recommended three doses of vaccine have antibody levels in the protective range at 9 to 12 months, regardless of gestational and birthweight [5]. Safe for use in infants born to HIV-positive mothers, although it may be less effective [6].

Administration

The vaccine may be administered subcutaneously in patients at risk for hemorrhage following IM injection, but the immune response may be lower [1][2][4].
A 22- to 25-gauge needle should be used. The appropriate needle length is 7/8" to 1" for infants [4].

MEDICATION SAFETY

Contraindications/Precautions

Contraindicated in patients with a serious allergic reaction (eg, anaphylaxis) after a previous vaccine dose or to a component of the vaccine, including yeast [7].

Vaccination should be deferred in patients with moderate or severe acute illness, with or without fever. Immunocompromised patients may have a suboptimal response to the vaccine [8].
Apnea may occur in some premature infants following IM administration [7].
Syncope, at times associated with **other neurologic signs** (such as tonic-clonic movements, paresthesias) may occur with the administration of injectable vaccines, including hepatitis B vaccine [9].
Available evidence suggests that hepatitis B vaccination is not associated with an increased risk for development or relapse of multiple sclerosis [9].
Latex-sensitive individuals; use caution as the tip caps of the prefilled Engerix-B® syringes may contain natural rubber latex [10].

Adverse Effects

The only common side effect is soreness at the injection site. Fever greater than 37.7 degrees C occurs in 1% to 6%.

Monitoring

Testing for immunity 3 months after completion of the vaccination series is recommended for infants born to HBsAg-positive mothers [4] and, perhaps, for premature infants who received an early first dose.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Recombinant hepatitis B vaccines are produced by *Saccharomyces cerevisiae* (common baker's yeast) that has been genetically modified to synthesize HBsAg. Both vaccines are inactivated (noninfective) products that contain HBsAg protein adsorbed to aluminum hydroxide, and may be interchanged with comparable efficacy [1][2].

ABOUT

Special Considerations/Preparation

Recombivax HB® for infant use is supplied in 0.5-mL single-dose vials and single-dose prefilled syringes containing 5 mcg. Engerix-B® is supplied as 10-mcg/0.5 mL and 20-mcg/1 mL strengths. Preservative free. The vaccine should be used as supplied; do not dilute. The tip caps of the prefilled Engerix-B® syringes may contain natural rubber latex. **Shake well before withdrawal and use.** Store refrigerated at **2 to 8 degrees C (36 to 46 degrees F)**. **Do not freeze**-destroys potency [10][1].

Hib Conjugate/Hepatitis B Combination Vaccine

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Do not administer to any infant before 6 weeks of age[1]
0.5 mL IM in the anterolateral thigh [1].

Please refer to the most recent AAP/ACIP immunization schedule. It is recommended that premature infants should be immunized according to their postnatal age; some data, however, suggest delaying the first dose in chronically ill premature infants due to inadequate seroconversion against *H influenzae*.

Uses

Complete immunization schedules and guidance can be found at the following link: https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html

Comvax® is indicated for vaccination against invasive disease caused by *Haemophilus influenzae* type b and against infection caused by all known subtypes of hepatitis B virus in infants 6 weeks to 15 months of age born to HBsAg-negative mothers. Comvax® should not be used in infants younger than 6 weeks of age [1].

Administration

When giving multiple vaccines, use a separate syringe for each and give at different sites. Care should be taken to draw back on the plunger of the syringe before injection to be certain the needle is not in a blood vessel [1].

MEDICATION SAFETY

Contraindications/Precautions

Contraindicated in patients with a serious allergic reaction (eg, anaphylaxis) after a previous vaccine dose or to a component of the vaccine. Also **contraindicated** in infants less than 6 weeks of age (due to Hib component). Vaccination should be deferred in patients with moderate or severe acute illness, with or without fever. Immunocompromised patients

may have a suboptimal response to the vaccine [2].

Adverse Effects

Fever, irritability, somnolence, and injection site reactions (ie, local erythema, swelling, and tenderness) are common. Rare anaphylactic reactions (ie, hives, swelling of the mouth, hypotension, breathing difficulty, and shock) have been reported [1].

Monitoring

Observe injection site for local reactions.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Comvax® (preservative-free) combines the antigenic components of Recombivax HB® and PedvaxHIB®. Each 0.5 mL dose contains 5 mcg HBsAg and 7.5 mcg *Haemophilus b*-PRP (conjugated to meningococcal protein). Immune response is produced through formation of protective antibodies (anti-HBs) and formation of a T-dependent antigen from the PRP-conjugate that stimulates an enhanced antibody response and immunologic memory [1].

ABOUT

Special Considerations/Preparation

Supplied in 0.5-mL single-dose vial. Store refrigerated. **Do not freeze**[1].

Hyaluronidase

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Dispersion and absorption of injected drugs:
150 units (range 50 to 300 units) subQ before administration of other drugs or added to the injected solution of other injected or subQ infused drugs [1][2][3].

Extravasation: Inject 1 mL (150 units) as 5 separate 0.2-mL subQ injections around the periphery of the extravasation site. Use 25- or 26-gauge needle and change after each injection [4][5][6].
Alternatively, dilute 0.1 mL hyaluronidase (150 units/mL) with 0.9 mL of normal saline to give a concentration of 15 units/mL. Inject as 5 separate 0.2-mL subQ injections around the periphery of the extravasation site. Use 25- or 26-gauge needle and change after each injection [7][8][9][10][11][12].

Hypodermoclysis:
1 mL (150 units of Hylenex® product) subQ prior to infusion of fluids. Anatomical areas of subQ fluid administration included mid-anterior thigh or interscapular area of the upper back [1][13]. Rate and volume of rehydration fluids should not exceed those appropriate for IV fluid administration [1].

Urographic contrast media injection, adjunct:
75 units subQ over each scapula, followed by injection of the contrast medium at the same site [1][2].

Uses

Prevention of tissue injury caused by IV extravasation. Suggested indications (some anecdotal) are for extravasations involving drugs that are irritating to veins because of hyperosmolarity or extreme pH (e.g. aminophylline, amphotericin B, calcium, diazepam, erythromycin, gentamicin, methicillin, nafcillin, oxacillin, phenytoin, potassium chloride, rifampin, sodium bicarbonate, tromethamine, vancomycin, and TPN, and concentrated IV solutions) [4][8][14][9][10][16][11][12][19]. Hyaluronidase is not indicated for treatment of extravasations of vasoconstrictive agents (eg, dopamine, epinephrine, and norepinephrine) [3].

Pediatric FDA Approved Indications
Adjuvant in subcutaneous fluid administration for achieving hydration [1][2][3]. Human recombinant product (Hylenex®) is preferred over animal derived products in children to decrease potential for allergic reactions [13].
Adjuvant to increase dispersion and adsorption of other injectable agents [1][2][3].

Adjunct in subcutaneous urography to improve resorption of radiopaque agents [1][2][3].

Administration

Extravasation
Use at concentrations of 15 units/mL [7][8][9][10][11][12] or undiluted at 150 units/mL [4][5][6].
Increase therapeutic success:
1) Initiating treatment within 1 to 2 hours of extravasation [7][10]; however benefit may be observed with administration as long as 10 days after extravasation incident [7].
2) Elevate extremity, place saline soaked gauze over the area, and gently squeeze out fluid from the open insertion site [7].
3) Covering with a hydrogel/hydrocolloid dressing [7][8][14][15][9][16].

Hypodermoclysis
When administering fluids by subQ route, do not exceed the rate and volume of fluids administered by IV route. The **maximum volume of fluids is 25 mL/kg at a rate no faster than 2 mL/min** for premature or full-term infants [1]. Hyaluronidase may be added to small volumes of solutions (up to 200 mL) or solutions of subQ drugs [2].

Hydase TM
May be administered for infiltration use, interstitial use, intramuscular use, intraocular use, retrobulbar use, soft tissue use, or subcutaneous use [17].

Hylenex
Do not administer IV. May be administered for infiltration, interstitial, IM, intraocular, peribulbar, retrobulbar, soft tissue, or subQ use [18].

MEDICATION SAFETY

Contraindications/Precautions

Precautions
Not recommended for IV use. Discontinue use if sensitization occurs. Should not be used to enhance the absorption and dispersion of dopamine and/or alpha agonist agents. Do not inject near area of infection or acutely inflamed area because of the risk of spreading a localized infection [17][1].
To rule out a potential hypersensitivity reaction, a skin test (0.02 mL intradermally of a 150 unit/mL or 200 unit/mL of hyaluronidase) may be performed [17][1][2][3].
Hylenex® contains albumin; therefore, there is a rare chance for transmission of viral and variant Creutzfeldt-Jakob disease [1].

Adverse Effects

The most frequent adverse events reported are injection site reactions. Allergic reactions have occurred rarely [1].

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Incompatibility

Benzodiazepines, epinephrine, furosemide, heparin, and phenytoin.

Monitoring

No specific monitoring required.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Hyaluronidase is a mucolytic enzyme that disrupts the normal intercellular barrier and allows rapid dispersion of extravasated fluids through tissues.

ABOUT

Special Considerations/Preparation

Vitrase® and Hydase™ are purified animal-derived (ovine and bovine, respectively) hyaluronidase [17], and Hylenex® is a recombinant human hyaluronidase.
Hydase™ contains 1 mg edetate disodium [17]. Hylenex® contains 0.9 mg edetate disodium [1][3].
Hydase™ and Hylenex® are supplied as 150 USP units/mL in single-use glass vials. Vitrase® is supplied as 200 USP units/mL in single-use glass vials.

Hyaluronidase products: Store refrigerated; do not freeze [17]. Protect Vitrase® from light [1][2][3].

HydrALAZINE

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Parenteral: Begin with 0.1 to 0.5 mg/kg/dose IV every 6 to 8 hours. Dose may be gradually increased as required for blood pressure control to a maximum of 2 mg/kg/dose every 6 hours.
Oral: 0.25 to 1 mg/kg/dose orally every 6 to 8 hours, or approximately twice the required IV dose. Administer with food to enhance absorption.

Note: Use with a beta-blocking agent is often recommended to enhance the antihypertensive effect and decrease the magnitude of the reflex tachycardia. This is expected to reduce hydrALAZINE IV dosage requirements to less than 0.15 mg/kg per dose.

Uses

Treatment of mild to moderate neonatal hypertension by vasodilation. Afterload reduction in patients with congestive heart failure.

Administration

Intravenous: Administer undiluted (20 mg/mL) [1] over 30 seconds [2] to 2 minutes [3]. Further dilution (ie, 1 mg/mL) may be necessary.

MEDICATION SAFETY

Adverse Effects

Diarrhea, emesis, and temporary agranulocytosis have been reported in neonates. Tachycardia, postural hypotension, headache, nausea, and a lupus-like syndrome occur in 10% to 20% of adults. Uncommon reactions in adults include GI irritation and bleeding, drug fever, rash, conjunctivitis, and bone marrow suppression.

Solution Compatibility

NS.

Terminal Injection Site Compatibility

Dobutamine, heparin, hydrocortisone succinate, and potassium chloride.

Terminal Injection Site Incompatibility

Aminophylline, ampicillin, diazoxide, furosemide, and phenobarbital.

Monitoring

Frequent assessment of blood pressure and heart rate. Guaiac stools. Periodic CBC during long-term use.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Causes direct relaxation of smooth muscle in the arteriolar resistance vessels. Major hemodynamic effects: Decrease in systemic vascular resistance and a resultant increase in cardiac output. Increases renal, coronary, cerebral, and splanchnic blood flow. When administered orally, hydrALAZINE has low bioavailability because of extensive first-pass metabolism by the liver and intestines. The rate of enzymatic metabolism is genetically determined by the acetylator phenotype--slow acetylators have higher plasma concentrations and a higher incidence of adverse effects.

ABOUT

Special Considerations/Preparation

HydrALAZINE hydrochloride injection for IV use (20 mg/mL) is available in 1-mL vial. A 1-mg/mL dilution may be made by diluting 0.5 mL of the 20-mg/mL concentrate with 9.5 mL

of preservative-free normal saline for injection.

Oral
Oral tablet strengths include 10, 25, 50, and 100 mg [4].

Oral Extemporaneous Compound
HydrALAZINE hydrochloride 4-mg/mL oral liquid prepared in a 1:1 mixture of Ora-Sweet SF®/Ora-Plus® was only stable (less than 10% loss of potency) for 2 days under refrigeration (5 degrees C) and only 1 day when prepared with Ora-Sweet®/Ora-Plus®. It was not stable when mixed with cherry syrup or when stored at room temperature. The authors suggest that preparing a small quantity (enough for 24 hours) may be the most appropriate method to ensure stability [5].

HydrALAZINE hydrochloride 1-mg/mL oral aqueous solutions were stable in mannitol and sorbitol (0.24 molar) for 21 days (less than 10% loss of potency) at room temperature. Oral formulations using simple syrups containing dextrose, fructose, sucrose, or maltose were unstable. The addition of phosphate and citrate buffers to the solution had no adverse affect on the vehicle stability[6].

HydroCHLOROthiazide

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

1 to 2 mg/kg/dose orally every 12 hours.
Administer with food (improves absorption).

Note: Do not confuse with chlorothiazide.

Uses

Bronchopulmonary dysplasia (BPD): May improve pulmonary function in patients with BPD.

Edema and Hypertension: Diuretic used in treating both mild to moderate edema and mild to moderate hypertension. Effects increased when used in combination with furosemide or spironolactone.

Heart Failure: In neonates with pulmonary hypertension, supportive care with diuretics may be used cautiously for signs of right-sided heart failure [1].

MEDICATION SAFETY

Adverse Effects

Hypokalemia and other electrolyte abnormalities. Hyperglycemia. Hyperuricemia.
Do not use in patients with significant impairment of renal or hepatic function.

Monitoring

Serum electrolytes, calcium, phosphorus, and glucose; urine output and blood pressure.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Limited data in neonates. Rapidly absorbed from GI tract. Onset of action is within 1 hour. Elimination half-life depends on GFR and is longer than that of chlorothiazide. Major diuretic effect results from inhibition of sodium reabsorption in the distal nephron. Increases urinary losses of sodium, potassium, magnesium, chloride, phosphorus, and bicarbonate. Decreases renal excretion of calcium. Inhibits pancreatic release of insulin. Displaces bilirubin from albumin.

ABOUT

Special Considerations/Preparation

Supplied as 12.5-mg capsule and 25-, 50-, and 100-mg tablets.

Spironolactone/hydroCHLOROthiazide 5-mg/5 mg per mL oral solution can be prepared by using 24 tablets of spironolactone/**hydroCHLOROthiazide** 25 mg/25 mg in 120 mL of either a 1:1 mixture of Ora-Sweet® and Ora-Plus®, a 1:1 mixture of Ora-Sweet SF® and Ora-Plus®, or cherry syrup (cherry syrup concentrate diluted 1:4 with simple syrup). Crush tablets to a fine powder, add 25 mL of vehicle, and mix to create a uniform paste. Add vehicle to almost volume, transfer to amber bottle and add vehicle to final volume of 120 mL. Label "shake well" and "protect from light", with expiration date of 60 days. In the stability study, at least 91% of the initial **hydroCHLOROthiazide** and spironolactone concentration was retained for up to 60 days when stored without light at 5 and 25 degrees C [2].

DOSING/ADMINISTRATION

Dose

Oral Route

Adrenocortical Insufficiency

Initial: 8 to 10 mg/m^2/day orally in 3 divided doses administered 3 times daily. Round the dose to the nearest 0.5 mg or 1 mg, and use the contents of more than 1 capsule if necessary. Higher starting doses may be needed based on patient's age and symptoms of the disease. Lower starting doses may be sufficient in patients with residual but decreased endogenous cortisol production [1].

Dosage titration: Adjust doses based on signs and symptoms of under- or overtreatment, including adrenocortical insufficiency, linear growth, and weight gain. Individualize the dose, and use the lowest possible dosage. Increased doses may be needed during episodes of acute febrile illness, gastroenteritis, and surgery or major trauma [1].

Switching from another oral product: Use the same total daily dosage. If symptoms of adrenal insufficiency occur after switching, increase the total daily dosage [2].

Physiologic replacement: 7 to 9 mg/m^2 per day orally or IV, in 2 or 3 doses.

Dose Adjustments, Oral

Renal impairment: Hydrocortisone and its metabolites are excreted in the urine [1]

Hepatic impairment: Hydrocortisone is metabolized in the liver and most body tissues [1]

Periods of stress (infections, surgery): Increase the dose [1]

Vomiting, severely ill, or unable to take oral medications: Switch to parenteral corticosteroid formulations without delay; gradually reduce the steroid dose used during the acute event once the patient recovers [1].

Intravenous Route

Chronic Lung Disease (CLD)

Routine use of postnatal corticosteroids is currently not recommended by the American Academy of Pediatrics. However, the decision to use corticosteroids to prevent or treat CLD should be individualized to each patient and discussed with the parents [3].

Dosage: 5 mg/kg/day IV in 4 divided doses for 7 days, 3.75 mg/kg/day in 3 divided doses for 5 days, then subsequently lowering the frequency by 1 dose every 5 days (cumulative dose of 72.5 mg/kg over 22 days) [4]

Low dose: 0.5 mg/kg/dose IV every 12 hours for 7 days, followed by 0.5 mg/kg/day IV for 3 days [5]

Congenital Adrenal Hyperplasia (CAH):

Maintenance dosage: 10 to 15 mg/m^2/day orally given in 3 divided doses [6].

Stress dosage for adrenal crisis

• **Infants and preschool age children:** Initial IV dose, 25 mg IV; successive doses of 6.25

mg IV every 6 hours may be given. Resume maintenance dosage once patient is stable [6].

Physiologic replacement: 7 to 9 mg/m^2 per day IV or orally, in 2 or 3 doses.

Treatment of pressor- and volume-resistant hypotension (Stress doses):
20 to 30 mg/m^2 per day IV, in 2 or 3 doses, or approximately 1 mg/kg per dose every 8 hours.

Body Surface Area	
Weight (kg)	**Body Surface Area (m(2))**
0.6	0.08
1	0.1
1.4	0.12
2	0.15
3	0.2
4	0.25
BSA (m(2)) = (0.05 x kg) + 0.05	

Treatment of chorioamnionitis-exposed ELBW infants to decrease risk of CLD:
Initial dose: 0.5 mg/kg/dose IV every 12 hours for 12 days, followed by 0.25 mg/kg IV every 12 hours for 3 days [7].

Uses

Chronic Lung Disease (CLD) - AAP Guidelines
• High dose postnatal corticosteroids (PCS) are not recommended to prevent or treat CLD in preterm infants [3].
• Routine use of PCS is currently not recommended by the American Academy of Pediatrics. However, the decision to use corticosteroids to prevent or treat CLD should be individualized to each patient and discussed with the parents [3].
• If PCS is given, a low dose given for a short, predetermined duration (eg, extubation) is recommended. If an infant does not show clinical response to PCS within 72 hours, continued treatment is not recommended [3].
• Dexamethasone and hydrocortisone are the most studied and used PCS for treating infants with CLD. Inhaled corticosteroids do not appear to offer any advantages to systemic corticosteroids [3].
• Indomethacin should not be used concurrently with PCSs [3].

A composite outcome of death or BPD at 36 weeks' postmenstrual age was not different between hydrocortisone started between 7 and 14 days after birth and placebo (70.7% vs 73.7%; adjusted OR 0.87 (95% CI, 0.54 to 1.38; p = 0.54)) in a randomized double-blinded trial (n=372). The median gestational age was 25.4 weeks (24.9 to 26.4 weeks) for the hydrocortisone group and 25.6 weeks (24.7 to 26.4 weeks) for the placebo group. Hydrocortisone sodium succinate dosage was 5 mg/kg/day in 4 divided doses for 7 days, 3.75 mg/kg/day in 3 divided doses for 5 days, then subsequently lowering the frequency by 1

dose every 5 days (cumulative dose of 72.5 mg/kg over 22 days) [4].
Although, a double-blind, randomized, multicenter trial (n=521) demonstrated that more neonates (24 to 27 weeks of gestation) administered low-dose hydrocortisone during their first 10 postnatal days survived to 36 weeks of postmenstrual age without bronchopulmonary dysplasia compared with placebo (60% vs 51%; OR, 1.48 (95% CI, 1.02 to 2.16)). The hydrocortisone dose was 0.5 mg/kg/dose IV every 12 hours for 7 days, followed by 0.5 mg/kg/day IV for 3 days. The rate of gastrointestinal perforation was 5% for the hydrocortisone group and 4% for the placebo group [5]. Degree of neurodevelopmental impairment was not significantly different between the hydrocortisone and placebo groups (no impairment, 73% vs 70%; mild impairment, 20% vs 18%; moderate to severe impairment, 7% vs 11%) in 379 children who were evaluated at a median 22 months' corrected age. Other major neurodevelopmental outcomes, including cerebral palsy, were also not significantly different between groups [10]. [11]. At a 2 year follow-up, better global neurodevelopmental outcomes were associated with the 24 and 25 weeks' gestational age group receiving hydrocortisone compared with placebo. In contrast, there was no difference between hydrocortisone and placebo in the 26 and 27 weeks' gestational age group [11]. Longer-term safety remains to be evaluated [12].
In a randomized, placebo-controlled clinical trial of ELBW neonates receiving low-dose hydrocortisone or placebo (started within the first 48 hours of life), babies exposed to chorioamnioitis receiving hydrocortisone had significantly improved survival without BPD and decreased mortality before 36 weeks PMA when compared to those receiving placebo (OR 2.84; 95% CI, 1.21 to 6.67). There were no differences in these outcomes for infants without chorioamnioitis exposure receiving hydrocortisone when compared with placebo (OR 0.72; 95% CI, 0.31 to 1.65). The trial was stopped early due to an increased incidence of spontaneous GI perforation in the group receiving hydrocortisone (calculated sample size=712 births; actual final enrollment=360 births) [7].

Congenital adrenal hyperplasia (CAH) Hydrocortisone is the preferred glucocorticoid treatment option during childhood over other longer acting glucocorticoids. Hydrocortisone has a shorter half-life, which lowers the risk of adverse effects compared with other glucocorticoids, including growth suppression. Crushed tablets mixed with a small amount of water are recommended over liquid preparations [6].

Pressor- and volume-resistant septic shock Sepsis guidelines suggest hydrocortisone treatment only in newborns with adrenal insufficiency [13].

FDA Approved Pediatric Indication
Hydrocortisone oral granules are indicated as replacement therapy in pediatric patients with adrenocortical insufficiency [1].

Administration

Intravenous:
• Administer over a period of 30 seconds (eg, 100 mg) to 10 minutes (eg, 500 mg or more). The reconstituted solution (50 and 125 mg/mL) may be given without further dilution. For intravenous infusion, may dilute to 1 mg/mL in D_5W or NS for infusion [8]. The preferred concentrations are 50 mg/mL for intermittent IV (bolus) and 1, 2, 5 mg/mL intermittent IV

(infusion) [9].

Oral
Tablet
• Guideline recommendations for congenital adrenal hyperplasia suggest crushing the tablet formulation and mixing with small amount of liquid just prior to administration. This method of administration is preferred over the use of liquid formulations [6].
Granules
• Hold the capsule so that the printed strength is at the top and tap the capsule to ensure all the granules are in the lower half of the capsule [1].
• Squeeze the bottom of the capsule gently and twist off the top of the capsule [1].
• Pour the granules directly onto the patient's tongue, onto a spoon and place in the patient's mouth, or sprinkle the granules on a spoonful of cold or room temperature soft food (eg, yogurt, fruit puree). The granules should be given and swallowed within 5 minutes to avoid a bitter taste [1].
• Tap the capsule to ensure all the granules are removed, and avoid getting the capsule wet on the tongue or soft food as granules may remain in the capsule [1].
• After granules are given, immediate give fluids (eg, water, milk, breast milk, formula) to ensure all granules are swallowed [1].
• Do not swallow capsules, chew or crush the granules, or add granules to liquid. Do not use granules in nasogastric or gastric tubes, as they may block the tube [1].

MEDICATION SAFETY

Contraindications/Precautions

Contraindications
Intrathecal administration and use in patients with systemic fungal infections is **contraindicated**. IM administration is contraindicated in patients with idiopathic thrombocytopenic purpura. Live and live, attenuated vaccines are contraindicated in patients receiving immunosuppressive doses of corticosteroids [16][17]. **A-Hydrocort®** contains benzyl alcohol and is **contraindicated** in premature infants [18].

Precautions
Endocrine and metabolic: Pheochromocytoma crisis has been reported and may be fatal. Consider risk prior to initiation [16][19].
Endocrine and metabolic: Adrenal crisis, potentially fatal, may occur with adrenal insufficiency caused by undertreatment, sudden discontinuation of therapy, or switching between oral formulations. Adrenal crisis may also be induced by stress events such as infections or surgery when patients require higher doses; dosage adjustment may be necessary [2].
Endocrine and metabolic: Growth retardation in pediatric patients may occur with long-term use of corticosteroids in excessive doses. Effects on linear growth are less likely when used as replacement therapy; monitoring recommended [1].
Endocrine and metabolic: Excessive doses and prolonged use of corticosteroids may cause Cushing's syndrome; monitoring recommended [1]
Gastrointestinal: Increased risk of gastrointestinal perforation in patients with certain

gastrointestinal disorders; use caution if there is a probability of impending perforation, abscess, or other pyogenic infections, diverticulitis, fresh intestinal anastomoses and active or latent peptic ulcer. Increased risk with concomitant use of NSAIDs; monitoring recommended in patients receiving corticosteroids and NSAIDs [1]
Immunologic: Corticosteroid use may increase the risk of infection and may mask signs of current infection. Corticosteroid use may also exacerbate systemic fungal infections. Avoid use in the presence of systemic fungal infections unless use is required to control drug reactions. Avoid local injection into previously infected sites [20].
Immunologic: Avoid exposure to chicken pox or measles in patients without a past history of disease due to the risk of a serious or fatal course of the disease. Consider prophylaxis with immunoglobulins or treatment with antiviral agents if exposure occurs [20].
Musculoskeletal: Inhibition of bone growth and the development of osteoporosis may occur [20].
Ophthalmic: Ophthalmic effects, including cataract, glaucoma or central serous chorioretinopathy, have been reported with prolonged use of corticosteroids in high doses; monitoring recommended. Refer to ophthalmologist for development of ophthalmic adverse reactions [1]
Psychiatric: Psychic derangements (ie, euphoria, mood swings, personality changes, severe depression) may occur and preexisting psychiatric problems may be exacerbated [20]. Increased risk with higher doses. Monitoring recommended [1]

Adverse Effects

Hyperglycemia, hypertension, salt and water retention. There is an increased risk of GI perforations when treating concurrently with indomethacin. There is also an increased risk of disseminated *Candida* infections.

Endocrine Effects

Abnormal response to both adrenocorticotropic hormone and cortisol secretion occurred in 12% of extremely low birthweight infants administered hydrocortisone for respiratory deterioration or circulatory collapse in a retrospective cohort study (n=58). IV hydrocortisone 1 to 5 mg/kg for one or more treatments was administered and if needed oral treatment with hydrocortisone 1 to 2.5 mg/kg/day (10 to 25 mg/m^2/day was continued until the infant stabilized. The cumulative IV and oral doses were 9 mg/kg and 68.1 mg/kg, respectively, for a duration period of 57.1 days [21].

Neurological Effects

Prolonged courses of hydrocortisone compared with no hydrocortisone treatment were associated with fine motor and language delay at 8 months corrected age (CA) and motor delay at 20 months CA in a retrospective study of extremely-low-birth-weight infants (n=175). The majority (88%) of hydrocortisone treatment was used as an adjunct to wean off the ventilator and 9% for treatment-resistent hypotension. Treatment solely for hypotension began at less than 72 hours of age whereas the median start of treatment for ventilator weaning only was 15 days. The mean duration of hydrocortisone therapy was 49 days [22].
Early, low-dose hydrocortisone treatment was not associated with increased cerebral palsy [23]. Treated infants had indicators of improved developmental outcome.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Acyclovir, amikacin, aminophylline, amphotericin B, ampicillin, atropine, aztreonam, calcium chloride, calcium gluconate, cefepime, chloramphenicol, clindamycin, dexamethasone, digoxin, dopamine, enalaprilat, epinephrine, erythromycin lactobionate, esmolol, famotidine, fentanyl, furosemide, heparin, hydralazine, insulin, isoproterenol, lidocaine, linezolid, lorazepam, magnesium, metoclopramide, metronidazole, morphine, neostigmine, netilmicin, nicardipine, oxacillin, pancuronium, penicillin G, piperacillin, piperacillin/tazobactam, potassium chloride, procainamide, propofol, propranolol, remifentanil, sodium bicarbonate, vecuronium and vitamin K_1.

Terminal Injection Site Incompatibility

Midazolam, nafcillin, pentobarbital, phenobarbital, and phenytoin.

Monitoring

Therapeutic Laboratory Monitoring

• **Congenital adrenal hyperplasia:** Goals of treatment are to achieve 17-hydroxyprogesterone levels at the upper limit of normal or slightly elevated; normal 17-hydroxyprogesterone levels may indicate overtreatment. Androstenedione level target is at or near normal for age and sex [6].

Therapeutic Physical Monitoring

• **Adrenocortical insufficiency:** Monitor for symptoms of under- or overtreatment, including signs and symptoms of adrenocortical insufficiency, linear growth, and weight gain, especially during times of stress (eg, infections or surgery when patients require higher doses of corticosteroids) and when switching from another oral hydrocortisone formulation [2].

Toxic Laboratory Monitoring

• Monitor electrolytes. Monitor blood or urine levels of cortisol and 17-hydroxyprogesterone [8][14][15]

• **Congenital adrenal hyperplasia:** Monitor for signs of excess glucocorticoids and inadequate androgen suppression [6]..

Toxic Physical Monitoring
• Measure blood pressure and blood glucose frequently during acute illness.
• Monitor for symptoms of under- or overtreatment, including signs and symptoms of adrenocortical insufficiency and weight gain [1]
• Monitor for signs and symptoms of infection [1].
• Monitor for signs and symptoms of Cushing syndrome every 6 months during treatment; patients younger than 1 year may require more frequent monitoring (eg, every 3 to 4 months) [1]
• Monitor for behavioral and mood disturbances [1]
• Monitor for blurred vision or other visual disturbances [1]
• Monitor growth [2].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Hydrocortisone is the main adrenal corticosteroid, with primarily glucocorticoid effects. It increases the expression of adrenergic receptors in the vascular wall, thereby enhancing vascular reactivity to other vasoactive substances, such as norepinephrine and angiotensin II. Hypotensive babies who are cortisol deficient (less than 15 mcg/dL) are most likely to respond, and blood pressure will increase within 2 hours of the first dose. Hydrocortisone also stimulates the liver to form glucose from amino acids and glycerol, and stimulates the deposition of glucose as glycogen. Peripheral glucose utilization is diminished, protein breakdown is increased, and lipolysis is activated. The net result is an increase in blood glucose levels. Renal effects include increased calcium excretion. The apparent half-life in premature infants is 9 hours.

Therapeutic Drug Concentrations
Peak concentration
Oral, single-dose, pediatric: 19.4 mcg/dL [1]
Time to peak concentration
Oral: 0.75 hour [1]

Absorption
Bioavailability
Oral: 87% [1]

Distribution
Protein binding: 90% or more [1]

Half-Life:
IV and oral: 1.5 hours [1]

ABOUT

Special Considerations/Preparation

Injection
Solu-cortef® does not contain benzyl alcohol [16].
Availability: Supplied as 2-, 2-, 4-, or 8-mL vials containing hydrocortisone sodium succinate 100, 250, 500, or 1000 mg, respectively [16].
Storage: Store unreconstituted product at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F). After reconstitution, store at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F) and protect from light. Discard solution if not used after 3 days [16].
Reconstitution
For **IV or IM injection**: Reconstitute vial with no more than 2 mL of bacteriostatic water for injection or bacteriostatic sodium chloride injection; may be given without further dilution [16]
or for **IV infusion**: First, reconstitute vial with no more than 2 mL bacteriostatic water for injection then further dilute as follows [16]:
Dilute the reconstituted **100-mg** solution by adding to 100 to 1000 mL of D5W, or if patient is not sodium restricted, NS or D5NS [16].
Dilute the reconstituted **250-mg** solution by adding to 250 to 1000 mL of D5W, or if patient is not sodium restricted, NS or D5NS [16]
Dilute the reconstituted **500-mg** solution by adding to 500 to 1000 mL of D5W, or if patient is not sodium restricted, NS or D5NS [16]
Dilute the reconstituted **1000-mg** solution by adding to 1000 mL of D5W, or if patient is not sodium restricted, NS or D5NS [16]
Diluted solutions are stable for at least 4 hours [16].
For administration of a **small volume** of fluid, 100 to 3000 mg of hydrocortisone sodium succinate for injection may be added to 50 mL of D5W, or if patient is not sodium restricted, to NS or D5NS [16]

Oral
Availability: 0.5-, 1-, 2-, and 5-mg oral granules contained in transparent capsules [1]
Storage: Store at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F). Protect from light. Once the bottle has been opened, use within 60 days [1].

Extemporaneous Oral Compound
A hydrocortisone **1 mg/mL** oral suspension was stable for up to 91 days with or without refrigeration. Crush and triturate ten 10-mg tablets in a mortar. Transfer to a beaker. Rinse mortar multiple times with 1:1 of Ora-Sweet and Ora-Plus and pour rinsings in beaker. Add sufficient quantity of Ora-Plus/Ora-Sweet for a final volume of 100 mL. Store in amber plastic prescription bottles [24].
A hydrocortisone **2 mg/mL** oral suspension was stable for up to 91 days with or without refrigeration. Crush and triturate ten 10-mg tablets in a mortar. Transfer to a beaker. Rinse mortar multiple times with 1:1 of Ora-Sweet and Ora-Plus and pour rinsings in beaker. Add sufficient quantity of Ora-Plus/Ora-Sweet for a final volume of 50 mL. Store in amber plastic

prescription bottles [24].
A hydrocortisone oral suspension (**2.5 mg/mL**; made from tablets, 250 mg total) prepared in a vehicle containing sodium carboxymethylcellulose (1 g), methyl hydroxybenzoate (0.02 g), propyl hydroxybenzoate (0.08 g), polysorbate 80 (0.5 mL), syrup BP (10 mL), citric acid monohydrate (0.6 g) and water to 100 mL was stable for at least 30 days when stored in the dark at room temperature (25 degrees C) and under refrigeration (5 degrees C). The vehicle was prepared by dissolving the methylhydroxybenzoate, propyl hydroxybenzoate, citric acid, and syrup in hot water. The cooled solution was triturated with the sodium carboxymethylcellulose and left overnight. Ground hydrocortisone tablets were triturated with polysorbate 80 and the vehicle was added; water was added to 100 mL [25].

DOSING/ADMINISTRATION

Dose

Closure of patent ductus arteriosus
Standard dose: 10 mg/kg orally or IV, followed by 5 mg/kg/dose at 24 and 48 hours [1][2]. A second course has been used [3].
High dose: 15 to 20 mg/kg orally followed by 7.5 to 10 mg/kg orally per day for a total of 3 doses [4]

Uses

Closure of patent ductus arteriosus (PDA): Long-term outcomes are not improved when preterm infants, younger than 14 days, are treated routinely for PDA. Treatment benefits when administered after 2 weeks of age or in high-risk infants in the first 2 postnatal weeks are unknown [8]. There are risks to NSAIDs and there is a high rate of spontaneous closure; therefore, treatment should be limited to select preterm newborns with symptomatic PDA [9][10]. At 36 weeks' postmenstrual age, there was no significant difference in mortality or moderate to severe bronchopulmonary dysplasia between NSAID treatment (initiated 2 to 28 days postnatally) and no treatment in a cohort of 12,018 preterm infants (gestational age 28 weeks or younger) with patent ductus arteriosus [11].

Multiple Courses: Closure rates were 71% (67/94), 40% (11/27), and 35% (5/14) after the first, second, and third courses, respectively, of oral ibuprofen in preterm neonates (mean gestational age, 30.6 weeks (24 to 36 weeks) and birth weight 1220 g (490 to 3000 g)) with hemodynamically significant PDA in a retrospective study (n=97). Adverse events (thrombocytopenia and/or renal function impairment (n=3)) occurred with the first course of ibuprofen [3].

Ibuprofen vs expectant therapy: Expectant therapy (no treatment initiated with the intention of closing the PDA) was noninferior to ibuprofen therapy in regard to the primary composite outcome of necrotizing enterocolitis, moderate-to-severe bronchopulmonary dysplasia, or death at 36 weeks' postmenstrual age in patients with PDA (N=273). A primary outcome occurred in 46.3% of patients in the expectant treatment group and 63.5% of patients in the ibuprofen treatment group. Moderate-to-severe bronchopulmonary dysplasia was identified in 33.3% in the expectant group and 50.9% in the ibuprofen group. There were no significant differences in the incidence of necrotizing enterocolitis, death, or other adverse effects [12].
Ibuprofen vs Indomethacin: PDA closure rates were similar for IV or oral ibuprofen and IV or oral indomethacin (RR 1.07, 95% CI 0.92 to 1.24) in a meta-analysis of 39 studies of preterm and/or low birth weight infants (N=2843 infants); however, ibuprofen was associated with a reduced duration of ventilator support (mean difference -2.35 days, 95% CI -3.71 to

-0.99) and reduced risk of necrotizing enterocolitis (NEC; RR 0.68, 95% CI 0.49 to 0.94), and oliguria (RR 0.28, 95% CI 0.14 to 0.54). Serum/plasma creatinine levels 72 hours post-treatment were significantly lower in the ibuprofen group (mean difference -8.12 micromol/L, 95% CI -10.81 to -5.43) but there was high heterogeneity between studies and the GRADE level of evidence was low. PDA closure rates were also similar for oral ibuprofen only compared with IV or oral indomethacin (RR 0.96, 95% CI 0.73 to 1.27) and the risk of NEC was decreased in patients receiving ibuprofen (RR 0.41, 95% CI 0.23 to 0.73). Long-term outcomes in infants receiving treatment are needed [4].

Acetaminophen vs Ibuprofen vs Indomethacin: Acetaminophen IV is as effective as indomethacin IV and ibuprofen (at standard doses) IV in the closure of PDA in preterm infants (gestational age less than 28 weeks) with hemodynamically significant PDA in a randomized study (n=300). After the first treatment course, the closure rates were 80%, 77%, and 81% for acetaminophen, ibuprofen, and indomethacin, respectively. Adverse effects (increase in serum creatinine and serum BUN and decrease in platelet count and urine output) were significantly more with ibuprofen and indomethacin than acetaminophen. Bilirubin significantly increased with ibuprofen. The mean birth weights were 1.1 kg, 1 kg, and 1.1 kg in the infants treated with acetaminophen, ibuprofen, and indomethacin, respectively [13].

High-Dose: In a systematic review and network meta-analysis of ibuprofen, indomethacin, and acetaminophen used in 68 randomized trials in 4,802 preterm infants, high-dose oral ibuprofen (15 to 20 mg/kg orally followed by 7.5 to 10 mg/kg orally every 12 to 24 hours for a total of 3 doses) was more likely to be associated with hemodynamically significant PDA closure compared with standard doses of IV ibuprofen (OR 3.59 (95% credible intervals (CrIs) 1.64 to 8.17)) or IV indomethacin (OR 2.35 (95% CrIs 1.08 to 5.31)) by indirect comparisons. High-dose oral ibuprofen significantly reduced the need for repeat pharmacotherapy compared with standard-dose IV ibuprofen (OR, 0.35) and placebo/no treatment (OR, 0.07) and the need for surgical PDA ligation compared with standard-dose IV ibuprofen (OR, 0.01) and placebo/no treatment (OR, 0). There were no significant differences between high-dose oral ibuprofen and any of the active comparators or placebo/no treatment in neonatal mortality, necrotizing enterocolitis, bronchopulmonary dysplasia, or intraventricular hemorrhage. Standard dosages were 10 mg/kg IV followed by 5 mg/kg IV every 12 to 24 hours for a total of 3 doses for ibuprofen and 0.1 to 0.3 mg/kg IV every 12 to 24 hours for a total of 3 doses for indomethacin [14]. There was a significantly lower risk of failure to close PDA after three doses of high-dose ibuprofen compared with standard-dose ibuprofen (RR 0.37, 95% CI 0.22 to 0.61) in a separate meta-analysis of 39 studies of preterm and/or low birth weight infants (N=2843 infants). There were no significant differences in other reported outcomes (eg, oliguria, intraventricular hemorrhage, chronic lung disease). High-dose ibuprofen was defined as 15 to 20 mg/kg orally followed by 7.5 to 10 mg/kg orally per day for a total of 3 doses [4].

Oral vs. IV: Standard doses of oral ibuprofen were more likely to be associated with hemodynamically significant PDA closure compared with the standard-dose IV ibuprofen (OR 2.22 (95% credible intervals (CrIs) 1.44 to 3.4)) and placebo/no treatment (OR 9.93 (95% CrIs 6.23 to 16.08)) in a systematic review and network meta-analysis of ibuprofen, indomethacin, and acetaminophen used in 68 randomized trials in 4,802 preterm infants. Standard doses of oral ibuprofen reduced the need for repeat pharmacotherapy compared with standard-dose IV ibuprofen (OR, 0.39) and placebo/no treatment (OR, 0.08). There were no significant differences between standard doses of oral and IV ibuprofen in the need for surgical patent ductus arteriosus ligation, neonatal mortality, necrotizing enterocolitis, bronchopulmonary dysplasia, or intraventricular hemorrhage. Standard dosages were 10 mg/kg IV or oral followed by 5 mg/kg IV or oral every 12 to 24 hours for a total of 3 doses

for IV ibuprofen [14]. There was a significantly lower risk of failure to close PDA after three doses of oral ibuprofen compared with IV ibuprofen (RR 0.38, 95% CI 0.26 to 0.56) in a separate meta-analysis of 39 studies of preterm and/or low birth weight infants (N=2843 infants). Serum/plasma creatinine levels 72 hours post-treatment were significantly lower in the oral ibuprofen group (mean difference -22.47 micromol/L, 95% CI -32.4 to -12.53) but there was high heterogeneity between studies and the GRADE level of evidence was low. There were no significant differences in other reported outcomes (eg, oliguria, intraventricular hemorrhage, chronic lung disease) [4].
Ibuprofen vs placebo: Placebo was non-inferior to ibuprofen treatment in regards to bronchopulmonary dysplasia (BPD) incidence or death (44% vs 50%; 95% CI -0.11 to 0.22), in a non-inferiority study in infants with PDA (N=146). The incidence rates of other adverse outcomes, such as IVH, retinopathy, and NEC, were not significantly different between study groups. The PDA closure rate was significantly higher with ibuprofen (34% vs 7%) in infants at GA 27 to 30 weeks but there was no difference in infants at GA 23 to 26 weeks (8% vs 2%). Additionally, there were no differences between the ibuprofen and placebo groups in regards to PDA closure before discharge (89% vs 82%) and the follow-up closure rate (3% vs 6%) [15]. In full-term infants (n=51; older than 3 days of life), oral ibuprofen had a higher PDA closure rate compared with placebo (73.3% vs 42.9%) [2].

Prevention of patent ductus arteriosus (PDA): The risks do not outweigh the short-term benefits of prophylactic ibuprofen. The incidence of PDA and the need for rescue treatment with cyclo-oxygenase inhibitors or surgical closure were reduced with prophylactic oral or IV ibuprofen compared with placebo or no intervention; however adverse effects (oliguria, increased serum creatinine concentrations, gastrointestinal hemorrhage) increased in a meta-analysis (9 trials; N=1070). Spontaneous closure in the control group was 58% by day 3 or 4. Compared with placebo or no intervention there was no differences for necrotizing colitis, mortality, any grade intraventricular hemorrhage, or chronic lung disease [16].
Hemodynamically significant PDA developed in 28% of extremely low birth weight preterm infants (n=46; less than 28 weeks gestational age and less than 1000 g) administered prophylactic oral ibuprofen within 12 to 24 hours after birth compared with 56% in a control group. However, the study was terminated early due to the high adverse event profile with ibuprofen [17].

Pediatric FDA Approved Indications
Oral: Reduction of fever in children 6 months of age and older. Treatment of mild to moderate pain in children 6 months of age and older. Treatment of signs and symptoms of juvenile arthritis [18].
Intravenous: Reduction of fever, management of mild to moderate pain, and management of moderate to severe pain as an adjunct to opioid analgesics in children 6 months of age or older [5].

Administration

Intravenous: Administer by intermittent IV infusion at a final concentration of 4 mg/mL or less [5] over 15 minutes [6][7]
Oral: Ibuprofen may be mixed with 0.5 mL milk and administered via oro-gastric tube [1].

MEDICATION SAFETY

Contraindications/Precautions

Contraindications
History of asthma, urticaria, or any other allergic-type reactions after taking aspirin or other NSAIDs [20]
In the setting of coronary artery bypass graft (CABG) surgery [20]

Precautions
Cardiovascular: Increased risk of serious cardiovascular (CV) thrombotic events including myocardial infarction and stroke, including fatalities, in patients with and without known CV disease or risk factors for CV disease; increase in risk has been reported with higher doses of NSAIDs. Monitoring recommended [20]
Cardiovascular: Avoid use in patients with a recent myocardial infarction due to risk of reinfarction, CV-related death, and all-cause mortality; if use is unavoidable, monitoring recommended [20]
Cardiovascular: New onset of hypertension or worsening of preexisting hypertension may occur and contribute to the increased incidence of cardiovascular events; patients taking ACE inhibitors, thiazide diuretics, or loop diuretics may have impaired response to therapies. Monitoring recommended [20].
Cardiovascular: Fluid retention and edema has been reported with NSAIDs [20]
Cardiovascular: Avoid use in patients with severe heart failure unless benefits outweigh the risks; if use is unavoidable, monitoring recommended [20]
Dermatologic: Serious skin reactions, including exfoliative dermatitis, Stevens-Johnson Syndrome, and toxic epidermal necrolysis, may occur without warning; discontinuation required at the first appearance of skin rash or other sign of hypersensitivity [20]
Endocrine and metabolic: Correct volume status in dehydrated or hypovolemic patients prior to initiation [20].
Endocrine and metabolic: Increases in serum potassium, including hyperkalemia, have been reported with NSAIDs [20].
Gastrointestinal: Serious gastrointestinal bleeding, ulceration, and perforation may occur with increased risk with longer duration of NSAID use, concomitant use of oral corticosteroids, aspirin, anticoagulants, or selective serotonin reuptake inhibitors, and poor general health status; monitoring recommended and if serious event suspected, initiate evaluation and treatment. Avoid administration of analgesic doses of more than one NSAID at a time [20]
Gastrointestinal: Increased risk for gastrointestinal bleeding in patients with advanced liver disease and/or coagulopathy [20]
Gastrointestinal: Avoid use in patients at higher risk of gastrointestinal adverse events (inflammation, bleeding, ulceration, and perforation) unless benefits outweigh risks; consider alternate therapies in high-risk patients and patients with active gastrointestinal bleeding [20]
Hematologic: Anemia has been reported with NSAIDs; monitoring recommended [20].
Hematologic: Bleeding events may occur with increased risk in patients with coagulation disorders or the concomitant use of warfarin, other anticoagulants, antiplatelet agents (eg,

aspirin), serotonin reuptake inhibitors, and serotonin norepinephrine reuptake inhibitors; monitoring recommended [20].
Hepatic: Elevations of ALT or AST (3x ULN) have been reported with NSAID use. Discontinue treatment if symptoms consistent with liver disease develop [20].
Hepatic: Rare, sometimes fatal cases of severe hepatic injury, including fulminant hepatitis, liver necrosis, and hepatic failure have been reported. Discontinue treatment if symptoms consistent with liver disease develop [20].
Immunologic: Anaphylactic reactions have been reported in patients with and without known hypersensitivity to ibuprofen and in patients with aspirin-sensitive asthma [20].
Immunologic: Cases of drug reaction with eosinophilia and systemic symptoms (DRESS), sometimes fatal or life-threatening, have been reported with NSAID use; discontinue treatment if condition occurs [20].
Immunologic: Diagnostic signs in detecting infection (inflammation and fever) may be diminished [20]
Neurologic: Aseptic meningitis with fever and coma has been reported with oral ibuprofen [20]
Ophthalmic: Blurred or diminished vision, scotomata, and changes in color vision have been reported with oral ibuprofen; discontinue treatment and refer to ophthalmologist for evaluation [20].
Renal: Renal papillary necrosis and other renal injury has been reported with long-term NSAID use [20]
Renal: Renal toxicity has been reported with NSAIDs, with increased risk with long-term administration and in patients with impaired renal function, dehydration, hypovolemia, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors or angiotensin II receptor blockers; monitoring recommended [20]
Renal: Acceleration of renal dysfunction in patients with preexisting renal disease may occur; monitoring recommended [20].
Renal: Avoid use in patient with advanced renal disease unless benefits outweigh risks; if use unavoidable, monitoring recommended [20].
Respiratory: Exacerbation of asthma symptoms may occur; monitoring recommended in patients with asthma and without known aspirin hypersensitivity [20]

Adverse Effects

Gastrointestinal bleeding (n=2), spontaneous intestinal perforation (n=2), and acute kidney failure (n=2) occurred in extremely low birth weight preterm infants (n=46) administered oral ibuprofen within 12 to 24 hours after birth for prevention of patent ductus arteriosus [17].
Spontaneous intestinal perforation, without signs of necrotizing enterocolitis, occurred in 2 very low birth weight infants treated with oral ibuprofen for patent ductus arteriosus. The perforations resolved with Penrose drainage [21].
Compared with placebo, IV ibuprofen substantially altered renal function in infants with birth weight of 1000 g or less and/or gestational age of 26 weeks or less in a randomized, double-blind trial (n=134). In contrast, renal function was not altered in infants with a birth weight greater than 1000 g and/or gestational age of greater than 26 weeks [22].
Preterm infants administered IV ibuprofen experienced a higher peak total serum bilirubin (9 mg/dL vs 7.3 mg/dL), greater need for phototherapy (95.3% vs 87.2%), and a longer

duration of phototherapy (94.3 hours vs 87.2 hours) compared with preterm infants not treated with ibuprofen in a retrospective analysis (n=706 infants; 30 weeks gestational age or less) [23].
There have been case-reports of pulmonary hypertension with oral ibuprofen [1].

Black Box Warning

Cardiovascular Thrombotic Events[20]

- Non-steroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use.
- Ibuprofen is contraindicated in the setting of coronary artery bypass artery (CABG) surgery.

Gastrointestinal Bleeding, Ulceration, and Perforation

- NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events.

Monitoring

Monitor for signs and symptoms of gastrointestinal bleeding. Monitor blood pressure. Monitor coagulation tests in patients on anticoagulants and those with coagulation disorders. Monitor serum transaminases for liver abnormalities [18]. Carefully monitor renal function [19].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Nonsteroidal anti-inflammatory drug (NSAID) that has anti-inflammatory, analgesic, and antipyretic activity [18].

Oral ibuprofen is well absorbed in preterm infants [24][25]. Mean AUCs range from 402 mcg/hr/mL [25] to 618 mcg/hr/mL [24] after a single 10 mg/kg oral dose compared with 524 mcg/hr/mL after IV ibuprofen lysine 10 mg/kg [26]. The respective mean Cmax values (Tmax) were 20.1 mcg/mL (3 hours) [25], 30.7 mcg/mL (8 hours) [24], and 43.5 mcg/mL (1 hour) [26]. The range of demographics for the preterm infants (n=46) were 25 to 34 weeks gestational age and 628 to 2210 g [24][25][26].
The half-life range was 15 to 43 hours [25][26] and was not dependent on gestational age [25]. Mean half-life, CL, and Vd were 43.1 hours, 9.49 mLxhr/kg, and 0.244 L/kg,

respectively, after the first dose in 13 infants (28.7 weeks gestational age and 1310 g). After the third dose, values were 26.8 hours, 10.8 mLxhr/kg, and 0.171 L/kg, respectively [26]. There was no correlation between PDA closure and ibuprofen concentrations (28.7+/-16.9 mg/L) on the fourth day in 46 extremely low birth weight preterm infants administered oral ibuprofen 10 mg/kg within 12 to 24 hours after birth followed by 5 mg/kg at 24 and 48 hours [17]. Similarly, no correlation was demonstrated with IV ibuprofen lysine 10 mg/kg followed by 5 mg/kg/day at 24 and 48 hours administered to 68 extremely low birth weight infants [27].

High-Dose Ibuprofen

Mean ibuprofen plasma levels in 70 preterm infants at 12 to 24 hours of life and less than 29 weeks gestation having significant PDA were 47.1 mg/L and 109.8 mg/L 15 minutes following a 10 mg/kg (n=35) or 20 mg/kg (n=35) dose of ibuprofen lysine, respectively. Twenty-four hours following a second and third dose of 5 mg/kg or 10 mg/kg, mean serum levels were 46.2 mg/L and 70.4 mg/L, respectively. In infants with successful closure of PDA (n=52), ibuprofen levels were 88.4+/-37.2 mg/L 15 minutes after the first dose and 65.3+/-23.4 mg/L 24 hours after the third dose compared with 43.2+/-35.2 mg/L and 39.5+/-22.1 mg/L, respectively, in infants having refractory PDA (n=18) [6].

Proposed dose regimens were confirmed by pharmacokinetic simulations to achieve an $AUC_{\text{after dose 1}}$ of greater than 600 mg/L/hr or $AUC_{\text{after dose 3}}$ of greater than 900 mg/L/hr for a predicted success of closing PDA of 94% in a population pharmacokinetic and pharmacodynamic study of 66 infants (25 to 34 weeks' gestation) administered ibuprofen lysine IV. The following were proposed ibuprofen dosage [7].

- 18 mg/kg IV followed by 9 mg/kg 24 and 48 hours later for infants between 108 to 180 hours postnatal age
- 14 mg/kg IV followed by 7 mg/kg 24 and 48 hours later for infants between 70 to 108 hours postnatal age,
- 10 mg/kg IV followed by 5 mg/kg 24 and 48 hours later for infants younger than 70 hours postnatal age

ABOUT

Special Considerations/Preparation

Available in an oral suspension at a concentration of 100 mg/5 mL. Shake well before using. Available in 200-mg (over the counter), 400-mg, 600-mg and 800-mg tablets [18].

Imipenem/Cilastatin

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Usual dose
Body weight 2 kg or less
1 week or younger: 20 mg/kg/dose IV every 12 hours [1].
Older than 1 week: 25 mg/kg/dose IV every 12 hours [1].
Body weight 1.5 kg or more
Younger than 1 week: 25 mg/kg/dose IV every 12 hours [2].
1 to 4 weeks of age: 25 mg/kg/dose IV every 8 hours [2].

Anthrax: meningitis or disseminated infection and meningitis cannot be ruled out (as part of a triple therapy regimen) [3]
32 weeks or more gestational age
0 to 1 week: 25 mg/kg/dose IV every 12 hours
1 to 4 weeks: 25 mg/kg/dose IV every 8 hours
Duration: 2 to 3 weeks or more until stable. Continue antimicrobial course of prophylaxis (usually oral therapy) for up to 60 days from onset of illness [3].

Anthrax; meningitis ruled out (as part of a combination regimen) [3]
32 up to 34 weeks gestational age
0 to 1 week: 20 mg/kg/dose IV every 12 hours
1 to 4 weeks: 25 mg/kg/dose IV every 12 hours
34 weeks gestational age or older
0 to 1 week: 25 mg/kg/dose IV every 12 hours
1 to 4 weeks: 25 mg/kg/dose IV every 8 hours
Duration: 2 to 3 weeks or more until stable. Continue antimicrobial course of prophylaxis (usually oral therapy) for up to 60 days from onset of illness [3].

Dose Adjustments
Renal: Not recommended in pediatric patients weighing less than 30 kg with renal impairment [2].

Uses

Anthrax[3]:

Systemic Anthrax when meningitis can be ruled out (IV)
Combination IV Therapy
- **Preferred:** Ciprofloxacin. *Alternatives in order of preference: meropenem, levofloxacin, imipenem/cilastatin, or vancomycin. If strains are penicillin-susceptible, then penicillin G*

(preferred) or ampicillin (alternative).

- **Plus**
- **Preferred:** Clindamycin. *Alternatives in order of preference: linezolid, doxycycline (not for neonates 37 weeks gestation or younger), or rifampin.*

Systemic Anthrax (meningitis or disseminated infection and meningitis cannot be ruled out) (IV)
Triple IV Therapy

- **Preferred:** Ciprofloxacin. *Alternatives in order of preference: levofloxacin or moxifloxacin*
- **Plus**
- **Preferred:** Meropenem. *Alternatives in order of preference: imipenem/cilastatin or doripenem. If strains are penicillin-susceptible, then penicillin G (preferred) or ampicillin (alternative).*
- **Plus**
- **Preferred:** Linezolid. *Alternatives in order of preference: clindamycin or rifampin or as a last resort, chloramphenicol*

Pediatric FDA Approved Indications
Not indicated in patients with meningitis because safety and efficacy have not been established[2]
Not recommended in pediatric patients with CNS infections because of the risk of seizures [2]
Intravenous:
Lower respiratory tract infections caused by *Staphylococcus aureus* (penicillinase-producing strains), *Acinetobacter* species, *Enterobacter* species, *Escherichia coli*, *Haemophilus influenzae*, *H parainfluenzae*, *Klebsiella* species, and *Serratia marcescens*[2].
Urinary tract infections (complicated and uncomplicated) caused by *E faecalis*, *S aureus* (penicillinase-producing strains), *Enterobacter* species, *E coli*, *Klebsiella* species, *Morganella morganii*, *P vulgaris*, *P rettgeri*, and *Pseudomonas aeruginosa*[5].

Intra-abdominal infections caused by *E faecalis*, *S aureus* (penicillinase-producing strains), *S epidermidis*, *Citrobacter* species, *Enterobacter* species, *E coli*, *Klebsiella* species, *M morganii*, *Proteus* species, *P aeruginosa*, *Bifidobacterium* species, *Clostridium* species, *Eubacterium* species, *Peptococcus* species, *Peptostreptococcus* species, *Propionibacterium* species, *Bacteroides* species including *B fragilis* and *Fusobacterium* species [2]. Imipenem-cilastatin is considered an appropriate single agent for pediatric patients with a complicated extra-biliary intra-abdominal infection [6].

Gynecologic infections caused by *E faecalis*, *S aureus* (penicillinase-producing strains), *S epidermidis*, *Streptococcus agalactiae* (Group B streptococci), *Enterobacter species*, *E coli*, *G vaginalis*, *Klebsiella* species, *Proteus* species, *Bifidobacterium* species, *Peptococcus* species, *Peptostreptococcus* species, *Propionibacterium* species, and *Bacteroides* species including *B fragilis*[2].

Bacterial septicemia caused by *E faecalis*, *S aureus* (penicillinase-producing strains), *Enterobacter species*, *E coli*, *Klebsiella* species, *P aeruginosa*, *Serratia* species, *Bacteroides* species including *B fragilis*[2].

Bone and joint infections caused by *E faecalis*, *S aureus* (penicillinase-producing strains), *S epidermidis*, *Enterobacter* species, *P aeruginosa*[2].

Skin and skin structure infections caused by *E faecalis*, *S aureus* (penicillinase-producing strains), *S epidermidis*, *Acinetobacter* species, *Citrobacter* species, *Enterobacter* species, *E coli*, *Klebsiella* species, *M morganii*, *P vulgaris*, *Providencia rettgeri*, *P aeruginosa*, *Serratia* species, *Peptococcus* species, *Peptostreptococcus* species, *Bacteroides* species including *B fragilis*, *Fusobacterium* species [2].

Endocarditis caused by *S aureus* (penicillinase-producing strains) [2].

Administration

Administer by IV infusion over 20 to 30 minutes at a concentration of 5 mg/mL or less [2][4].

MEDICATION SAFETY

Contraindications/Precautions

Contraindications
Contraindicated in patients with hypersensitivity to imipenem or cilastatin, or any component of the product. **Intramuscular dosage form contraindicated** in patients with hypersensitivity to local anesthetics of the amide type and in patients with severe shock or heart block, as the IM product is to be diluted with lidocaine.

Precautions
Concomitant use with valproic acid/divalproex sodium is not generally recommended; however, if Primaxin® is necessary, supplemental anticonvulsant therapy is recommended as increasing the dose of valproic acid or divalproex sodium may not be sufficient. Concomitant use with probenecid is not recommended. Avoid use with concomitant ganciclovir unless the benefits outweigh the risks [2][7].
Neurological: Imipenem is not recommended for the treatment of central nervous system (CNS) infections in pediatric patients due to the risk for seizures. Seizures occur most often in patients with meningitis [8], preexisting CNS pathology, renal dysfunction [9], and in patients receiving excessive doses [10].

Adverse Effects

Seizures occur frequently in patients with meningitis, preexisting CNS pathology, and severe renal dysfunction. Local reactions at the injection site and increased platelet counts are the most frequent adverse effects. Other reactions, including eosinophilia, elevated hepatic

transaminases, and diarrhea, also occur in more than 5% of patients.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Acyclovir, aztreonam, cefepime, famotidine, insulin, linezolid, midazolam, propofol, remifentanil, and zidovudine.

Terminal Injection Site Incompatibility

Amikacin, amiodarone, azithromycin, fluconazole, gentamicin, lorazepam, milrinone, sodium bicarbonate, and tobramycin.

Monitoring

Periodic CBC and hepatic transaminases. Assess IV site for signs of phlebitis.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action: Imipenem is a broad-spectrum carbapenem antibiotic combined in a 1:1 ratio with cilastatin, a renal dipeptidase inhibitor with no intrinsic antibacterial activity. Bactericidal activity is due to inhibition of cell wall synthesis.
Clearance: Clearance is directly related to renal function.
Half-life: Serum half-life of imipenem in neonates is 2.5 hours; the half-life of cilastatin is 9 hours.

ABOUT

Special Considerations/Preparation

Available: Powder for injection in 250-mg, and 500-mg vials.

Reconstitution and Storage: For IV injection, reconstitute with compatible diluent, shake well, and transfer contents of vials to 100 mL NS or D_5W, or dilute the patient-specific dose to a final concentration not to exceed 5 mg/mL. Reconstitute ADD-Vantage® vials with 100 mL supplied ADD-Vantage® diluent. When reconstituted with compatible diluent, solution is stable for 4 hours at room temperature, 24 hours refrigerated [5].

DOSING/ADMINISTRATION

Dose

Intramuscular(Gamastan® S/D (IMIG))
Measles exposure: 0.5 mL/kg IM within 6 days of exposure [1][2].

Intravenous
Isoimmune hemolytic disease (total serum bilirubin at or above escalation of care threshold): 0.5 to 1 g/kg/dose IV over 2 hours; may repeat in 12 hours if necessary [3].
Neonatal alloimmune thrombocytopenia: 1 g/kg/dose IV every day for 2 doses [4].
Measles exposure: 400 mg/kg IV within 6 days of exposure [1].
See "Special Considerations/Preparation" for product-specific information.

Dose Adjustment
Intravenous
Renal Impairment: See IVIG Product-Specific Administration table below for product-specific information. No specific recommendations for neonates; however, product specific recommendations apply to children and adults. General recommendations: reduce administration rate, use the lowest concentration, and consider using non-sucrose containing products (see Special Considerations/Preparation section) [5].

Uses

Isoimmune hemolytic disease : Immune globulin is recommended for isoimmune hemolytic disease in infants refractory to phototherapy (continued elevations in bilirubin or total bilirubin within 2 to 3 mg/dL of the exchange level) [4][14]. The efficacy of immune globulin was inconclusive for the treatment or prophylaxis of Rh or ABO hemolytic disease of the newborn in a meta-analysis (n=12 studies; 813 preterm and term infants) [15].

Measles exposure: Immune globulin, either IV or IM, is recommended in individuals with no evidence of immunity to measles. The IV immune globulin preparation is recommended in the following individuals [1]:

- Severely immunocompromised hosts regardless of immunologic or vaccination status, including the following:
- Patients with severe primary immunodeficiency
- Patients who have received a bone marrow transplant until at least 12 months after finishing all immunosuppressive treatment, or longer in patients who have developed graft-versus-host disease
- Patients on treatment for acute lymphoblastic leukemia within and until at least 6 months after completion of immunosuppressive chemotherapy
- Patients with HIV infection or AIDS who have severe immunosuppression defined as CD4+ T-lymphocyte percentage of less than 15% (all ages) and those who have not received the measles, mumps, rubella vaccine since receiving effective antiretroviral therapy.

Neonatal alloimmune thrombocytopenia: The recommendation to use immune globulin for neonatal alloimmune thrombocytopenia is conflicting [4].

Sepsis: Neither mortality nor major disability at the age of 2 years was reduced with adjunctive IV immune globulin administered to neonates with proven or suspected serious infection and weighing less than 1500 g in a double-blind, randomized, controlled trial (n=3493). The dose of IV immune globulin was 500 mg/kg followed by a second dose 48 hours later [16].

There is not enough evidence to use immune globulin for other conditions in neonates (**neonatal alloimmune neutropenia**, **parvovirus B19 infection**, and **Kawasaki disease**) [4].

Pediatric FDA Approved Indications
Intramuscular
Safety and effectiveness in pediatric patients have not been established [2].
Intravenous (vary by specific product)
For the treatment of primary immunodeficiency diseases (PIDD) [17][18][19][11][12][8][13]. Gammagard® Liquid, Gammagard® S/D, and Gammaplex® are approved in children 2 years of age and older for PIDD. Privigen® is approved in children 3 years of age or older for PIDD. Bivigam® is approved in children 6 years or older for PID.

For the treatment of idiopathic thrombocytopenic purpura (ITP) [11][20][8][9][13]. Privigen® is approved for ITP in patients 15 years of age or older.

Gammaked™ is approved for the treatment of inflammatory demyelinating polyneuropathy (CIDP) [11].

Gammagard® S/D is approved for the treatment of Kawasaki syndrome [18].

Subcutaneous
For the treatment of primary immunodeficiency disease in pediatric patients 2 years or older [17][21][22]. This includes, but is not limited to, common variable immunodeficiency, X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies [17][21].

Administration

IM immune globulin and IV immune globulin are not interchangeable.

Intramuscular:Do not administer by subQ or IV. Do not administer in the gluteal region. Administer in the anterolateral aspects of the upper thigh and deltoid muscle of the upper arm. Do not administer at the same time as measles vaccine [2].

Intravenous: Selection of product depends on osmolarity, pH, viscosity, volume administered, and sodium or sugar content [4]. Rate of administration varies by product; refer to the IVIG Product-Specific Administration table below for specific information [6][7][8][9][10][11][12][13].

IVIG Product-Specific Administration						
Brand	**Infusion Rate**	**Infusion Rate in Renal Disease/Thrombotic Complications**	**Filter/Flushing Compatibility**	**Sodium**	**pH**	**Osmolality (mOsmol/kg) or Osmolarity (mOsmol/L)**
Bivigam(R) 10% (Biotest)	Initial, 0.5 mg/kg/min (0.005	Minimum rate practicable.	No/Not available (infuse using a	0.1 to 0.14	4 to	less than 510 mOsmol/kg
sol'n = solution						

	mL/kg/min) for the first 10 minutes; increase by 0.8 mg/kg/min every 20 minutes if tolerated to a maximum of 6 mg/kg/min		separate line by itself)	Molar	4.6	
Carimune(R) NF (CSL Behring AG)	Use the 3% solution for the first infusion at initial rate of 0.5 mg/kg/min; increase to 1 mg/kg/min after 30 minutes; up gradually to a maximum of 3 mg/kg/min.	Maximum rate less than 2 mg/kg/min.	Optional (15 micron or higher)/D5W or NS	less than 20 mg NaCl/g protein	6.6	mOsmol/kg 3% 6% 9% 12% NS 498 690 882 1074 D5W 444 636 828 1020 SW 192 384 576 768
Flebogamma(R) 5% and 10% DIF (Grifols)	Initial, 0.01 mL/kg/min for the first 30 minutes; increase gradually to a maximum of 0.1 mL/kg/min for 5% solution and 0.08 mL/kg/min for 10% solution.	Minimum rate practicable.	Not required/ Not available	trace amounts	5 to 6	240 to 370 mOsmol/L
Gammagard liquid 10% (Baxter)	Primary Immunodeficiency: Initial, 0.5 mL/kg/hr (0.8 mg/kg/min) for 30 minutes. Increase gradually every 30 minutes up to 5 mL/kg/hr (8 mg/kg/min).	Minimum infusion rate practicable.	Filter optional/NS	no added sodium	4.6 to 5.1	240 to 300 mOsmol/kg
Gammagard S/D IgA < 1 mcg/mL (Baxter)	Initial, infuse 5% sol'n at rate of 0.5 mL/kg/hr; increase gradually to 4 mL/kg/hr if tolerated; subsequent infusion of 10% sol'n starts at 0.5 mL/kg/hr, increase to 8 mL/kg/hr as tolerated. Antecubital veins for 10% sol'n.	Maximum rate less than 4 mL/kg/hr of a 5% solution, or less than 2 mL/kg/hr of a 10% solution.	Yes (15 micron) /Not Available	8.5 mg/mL	6.8	5% 636 mOsmol/L; 10% 1250 mOsmol/L
GAMMAKED(TM) 10% (Grifols Therapeutics)	Initial (PI, ITP), 1 mg/kg/min; if tolerated, increase	Minimum rate practicable.	No/Yes D5W or NS	trace amounts	4 to 4.5	258 mOsmol/kg

sol'n = solution

	gradually to a maximum of 8 mg/kg/min. Initial (CIDP), 2 mg/kg/min for the first 30 minutes; if tolerated, increase gradually to a maximum of 8 mg/kg/min.					
Gammaplex(R) 5% Liquid (Bio Products Lab)	Initial, 0.01 mL/kg/min for 15 minutes; increase every 15 minutes to 0.08 mL/kg/min.	Minimum rate practicable.	Yes (15 to 20 micron)/ Not Available	30 to 50 mEq/L	4.8 to 5.1	420 to 500 mOsmol/kg (not less than 240)
Gamunex-C(R) 10% (Grifols)	Initial (PI, ITP), 1 mg/kg/min for the first 30 minutes; if tolerated, increase gradually to a maximum of 8 mg/kg/min. Initial (CIDP), 2 mg/kg/min for the first 30 minutes; if tolerated, increase gradually to a maximum of 8 mg/kg/min.	Minimum rate practicable.	No/D5W or NS	trace amounts	4 to 4.5	258 mOsmol/kg
Octagam 5% liquid (Octapharma)	Initial, 0.01 mL/kg/min (0.5 mg/kg/min) for first 30 minutes; if tolerated, increase to 0.02 mL/kg/min (1 mg/kg/min) for next 30 minutes; increase to 0.04 mL/kg/min (2 mg/kg/min) for the next 30 minutes if tolerated then can maintain rate up to 0.07 mL/kg/min (3.33 mg/kg/min).	Minimum rate practicable, not to exceed 3.33 mg/kg/minute.	Optional (0.2 to 200 micron)/ Not Available	not more than 30 mmol/L	5.1 to 6	310 to 380 mOsmol/kg
Octagam 10% (Octapharma)	Initial, 0.01 mL/kg/min (1 mg/kg/min) for the first 30 minutes; if tolerated, increase to 0.02 mL/kg/min (2 mg/kg/min) for the next 30 minutes; increase	Minimum rate practicable, not to exceed 3.33 mg/kg/minute.	Optional (0.2 to 200 micron)/NS or D5W	not more than 30 mmol/L	4.5 to 5.	310 to 380 mOsmol/kg

sol'n = solution

	to 0.04 mL/kg/min (4 mg/kg/min) for the next 30 minutes; If tolerated, increase to 0.08 mL/kg/min (8 mg/kg/min) for the next 30 minutes. Maximum, less than 0.12 mL/kg/min (12 mg/kg/min).					
Privigen(R) 10% liquid (CSL Behring AG)	Initial, 0.005 mL/kg/min (0.5 mg/kg/min) and increase gradually if tolerated. Maximum for PI, 0.08 mL/kg/min (8 mg/kg/min). Maximum for ITP, 0.04 mL/kg/min (4 mg/kg/min).	Minimum rate practicable.	No/D5W or NS	trace amounts	4.6 to 5	240 to 440 mOsmol/kg (approx. 320)
References: manufacturer package inserts and Siegel, 2014						
KEY: CIDP = chronic inflammatory demyelinating polyneuropathy; PI = primary immunodeficiency; ITP = immune thrombocytopenic purpura						
sol'n = solution						

MEDICATION SAFETY

Contraindications/Precautions

Contraindicated

Anaphylaxis or severe systemic reaction to human immunoglobulins [21][26][27][28][29][30][11][12][31][33] or to any component of the product [9], including polysorbate 80 [22]

Hereditary intolerance to fructose, including infants and neonates for whom sucrose or fructose tolerance has not been established [30]

Hyperprolinemia (type I or II); Hizentra(R) and Privigen(R) contain the stabilizer L-proline [22][33]

IgA deficiency with antibodies against IgA, and a history of hypersensitivity; IG products contain trace amounts of IgA [21][22][26][27][28][30][11][12][31][33][9]

Severe thrombocytopenia or any coagulation disorder which would contraindicate IM injections [34]

Precautions

Dosing: Expanded fluid volume may cause overload with high-dose regimens [30][11][9][33] for chronic idiopathic thrombocytopenic purpura in patients at increased risk of acute kidney injury, hemolysis, thrombosis, or volume overload [33].

Endocrine and metabolic: Falsely elevated glucose measurements may occur during therapy in diabetic patients because of the maltose ingredient. This increases the risk of masked hypoglycemic episodes and over administration of insulin, potentially causing life-threatening hypoglycemia [26].

Endocrine and metabolic: Hyperproteinemia, increased serum viscosity, and hyponatremia

may occur. Distinguish hyponatremia from pseudohyponatremia (decreased calculated serum osmolality or elevated osmolar gap) [26][27][28][30][11][12][33][31][9].
Endocrine and metabolic: Hyperproteinemia, increased serum viscosity, and hypernatremia or pseudohyponatremia may occur with Gammagard S/D due to amount of sodium in product [29].
Hematologic: Delayed hemolytic anemia may occur and acute hemolysis consistent with intravascular hemolysis has been reported [35]; severe hemolysis-related renal dysfunction, renal failure, and disseminated intravascular coagulation have been reported [21][22][27][29][30][11][12][31]; increased risk with high doses (2 g/kg or greater), non-O blood group, and underlying inflammation; monitoring recommended [35][21][22][27][29][30][11][12][31], especially in patients with preexisting anemia or cardiovascular or pulmonary compromise [35][25].
Immunologic: Severe hypersensitivity reactions have been reported. Increased risk in IgA deficiency with anti-IgA antibodies [35] or corn allergy. Discontinue use if condition occurs [21][22][26][27][28][29][30][11][12][31][33][34].
Immunologic: Infusion reactions (ie, fever, chills, nausea, and vomiting) may occur, especially with first dose or with treatment hiatus of more than 8 weeks. Adherence to dose and administration guidelines recommended [27][28].
Immunologic: Infectious agent transmission may occur, including viruses and theoretical risk of Creutzfeldt-Jakob disease, as well as unknown or emerging viruses and other pathogens [21][22][26][27][28][29][30][11][12][31][33][9][34].
Immunologic: A false positive skin test may occur when an intradermal injection of concentrated gamma globulin solution is administered; do not perform skin tests [2].
Neurologic: Aseptic meningitis syndrome (AMS) may occur. Increased risk with high doses (1 to 2 g/kg or greater) or rapid infusion. Discontinuation may be necessary [18][21][22][26][27][28][30][11][12][31][33][9]. Increased susceptibility to AMS may occur in patients with migraine history[26] or in female patients [18][21].
Renal: Acute renal dysfunction, renal failure, acute tubular necrosis, proximal tubular nephropathy, osmotic nephrosis, and death may occur with immune globulin products, especially those that contain sucrose. Dosage adjustment may be necessary, particularly in patients with increased risk (eg, developing renal dysfunction, preexisting renal insufficiency, diabetes mellitus, volume depletion, sepsis, paraproteinemia, or concomitant nephrotic drugs) [21][22].
Respiratory: Transfusion-related acute lung injury (noncardiogenic pulmonary edema) may occur, usually with presenting symptoms within 1 to 6 hours of treatment [21][22][26][27][28][29][30][11][12][31][33][9].
Laboratory Interference: False-positive readings may occur in assays dependent on detection of beta-D-glucans for diagnosis of fungal infection [17]

Adverse Effects

Intravenous: Rare cases of hypoglycemia, transient tachycardia, and hypotension that resolved after stopping the infusion have been reported. The risk of necrotizing enterocolitis may be increased in term and late preterm infants treated for isoimmune hemolytic jaundice. Animal studies have demonstrated reticuloendothelial system blockade when higher doses (greater than 1 g/kg) have been used. All donor units are nonreactive to HBsAg and HIV. The manufacturing process of these products now includes a solvent/detergent treatment to inactivate hepatitis C and other membrane-enveloped viruses.

Black Box Warning

Renal Dysfunction and Failure: Renal dysfunction, acute renal failure, osmotic nephrosis, and death have been reported. Increased risk with concomitant use of nephrotoxic drugs,

preexisting renal insufficiency, diabetes mellitus, volume depletion, sepsis, or paraproteinemia. Discontinuation may be necessary [25][26][27][28][29][12][30][31][11][9].
Renal dysfunction and acute renal failure are more common with use of immune globulin IV products that contain sucrose; glucose-free products include Bivigam(TM) [12], Flebogamma(R) 5% DIF [27], Flebogamma(R) 10% DIF [28], Gammaplex(R) [30], Gammagard Liquid(R) [31], Gammagard S/D [29], Gammaked(TM) [11], Gamunex(R)-C, [9], Octagam(R) 10% [26], Privigen(R) [25], and Hizentra(R) [22]

Thrombosis: Thrombosis may occur with immune globulin products. Risk factors may include prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hyperviscosity, and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors. For patients at risk of thrombosis, administer at the minimum dose and infusion rate practicable, ensure adequate hydration before administration, and monitor for thrombosis. Assess blood viscosity in patients at risk for hyperviscosity [25][21][2][32].

Monitoring

Intramuscular: Baseline assessment of blood viscosity should be considered in those at risk for hyperviscosity [2].

Intravenous: Monitor carefully the rate of infusion for the first and possibly the second infusion due to adverse effects. Monitor vital signs closely during infusion. Periodic assessment of CBC, renal function, and urine output is recommended during therapy. Monitor for signs of hemolysis and thrombotic events, especially in patients with known risk factors. Baseline assessment of blood viscosity should be considered in those at risk for hyperviscosity [23][24].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Intravenous
IVIG is a plasma-derived, concentrated form of IgG antibodies present in the donor population. Significant lot-to-lot variation of specific antibodies may occur with all products. No significant differences in clinical outcomes using the different products have been seen. All preparations are reported to contain more than 92% IgG monomers and a normal distribution of IgG subclasses. Total IgG titers in treated, septic neonates remain elevated for approximately 10 days.

ABOUT

Special Considerations/Preparation

Intramuscular
Available as 2 mL and 10 mL vials, preservative-free and latex-free [2].

Intravenous

Reconstitute lyophilized products with supplied diluent. DO NOT SHAKE vials; swirl gently to mix. All products are preservative free. DO NOT FREEZE; products that have been frozen should not be used. Shelf life varies, but is at least 2 years, when stored properly. Do not mix IVIG products from different manufacturers.

IVIG Preparations			
Brand	**Form**	**Sugar**	**Preparation/Storage /Stability**
Bivigam Liquid 10% (Biotest)	10% ready-for-use solution	None (glycine stabilized)	Store refrigerated. Should be at room temperature for administration. Use immediately once vial has been entered and discard any unused portion. Not recommended to be mixed with any other IVIG products, IV solutions, or medications. Do not shake (Bivigam®, 2014).
Carimune NF (CSL Behring AG)	3, 6, and 12 g lyophilized vials	1.67 g sucrose/g IVIG	Store at room temperature. Use immediately after reconstitution if prepared outside of sterile laminar air flow hood. Solution is stable for 24 hours with aseptic technique and continuous refrigeration. Compatible with NS and D5W. Do not shake (Carimune® NF, 2010).
Flebogamma 5% and 10% DIF (Grifols)	5% and 10% ready-for-use solution	50 mg/mL D-sorbitol	Store at room temperature. Use immediately once vial has been entered and discard any unused portion. Not recommended to be mixed with any other IV solutions or medications. Protect from light (Flebogamma® 5%, 2013; Flebogamma® 10%, 2013).
Gammagard Liquid 10% (Baxter)	10% ready-for-use solution	None (glycine stabilized)	Store at room temperature or refrigerated. Should be at room temperature during administration. Compatible with D5W (not compatible with NS). Protect from light and do not shake

			(Gammagard® Liquid, 2014).
Gammagard S/D IGA <1 mcg/mL (Baxter)	2.5, 5, and 10 g lyophilized vials	2% glucose	Store at room temperature. Use immediately (no more than 2 hours after reconstitution if prepared outside of sterile laminar air flow hood). Stable for 24 hours with aseptic technique and refrigeration. Discard any partially used vials. Do not mix with other IV solutions or medications. Do not shake (Gammagard® S/D, 2013).
Gammaked 10% (Grifols)	10% ready-for-use solution	None (glycine stabilized)	Store at room temperature or refrigerated. If refrigerated, allow vial to come to room temperature before administering. Use immediately once vial has been entered and discard any unused portion. Do not mix with other IV solutions or medications. Do not shake (Gammaked™, 2013).
Gammaplex 5% (Bio Products Lab)	5% ready-for-use solution	50 mg/mL D-sorbitol	Room temperature or refrigerated. If refrigerated, allow vial to come to room temperature before administering. Use immediately once vial has been entered; discard unused portion. Do not mix with other IV fluids or medications. Do not shake and protect from light (Gammaplex®, 2013).
Gamunex-C 10% (Grifols)	10% ready-for-use solution	None (glycine stabilized)	Room temperature or refrigerated. If refrigerated, allow vial to come to room temperature before administering. Use immediately once vial has been entered; discard unused portion. Vials pooled under aseptic conditions must be used within 8 hours. Packaging components

			are latex free. Compatible with D5W, but not with NS. Do not shake (Gamunex®, 2014).
Octagam 5% and 10% Liquid (Baxter)	5% ready-for-use solution and 10% ready-for-use solution	5%, 100 mg/mL maltose. 10%, 90 mg/mL maltose	Store at room temperature or refrigerated. If refrigerated, allow vial to come to room temperature before administering. Do Not dilute. Use immediately once vial has been entered; discard unused portion. Infuse within 8 hours if vials are pooled for large doses. Packaging components are latex free. Do not mix with other IV fluids or medications (Octagam 5%, 2009; Octagam 10%, 2014)
Privigen 10% (CSL Behring AG)	10% ready-for-use solution	None	Store at room temperature. Use immediately once vial has been entered and discard any unused portion. Contents of vials pooled under aseptic conditions must be used within 8 hours. Packaging components are latex free. Compatible with D5W. Protect from light and do not shake (Privigen®, 2011).

DOSING/ADMINISTRATION

Dose

Closure of Ductus Arteriosus:
Usually three IV doses per course, maximum two courses. Give at 12- to 24-hour intervals with close monitoring of urine output. If anuria or severe oliguria occurs, subsequent doses should be delayed [1].
Longer treatment courses may be used: 0.2 mg/kg every 24 hours for a total of 5 to 7 days.

PDA Closure Dose (mg/kg)			
Age at 1st dose	**1st**	**2nd**	**3rd**
<48 hours	0.2	0.1	0.1
2 to 7 days	0.2	0.2	0.2
> 7 days	0.2	0.25	0.25

Prevention of Intraventricular Hemorrhage (IVH) and Patent Ductus Arteriosus (PDA):
Premature infants: Usual doses, 0.1 to 0.2 mg/kg/dose IV every 12 to 24 hours beginning within the first 6 to 24 hours of birth for a total of 3 doses [2]. The optimal dose is unknown, but 0.1 mg/kg/dose IV every 24 hours for 3 doses may attenuate potential reductions in urinary output [3][4][5][6].
Administration before 6 hours of age compared with older than 6 hours of age was not associated with a lower incidence of intraventricular hemorrhage in a retrospective study (n=868 neonates with a birthweight of less than 1250 g) [7].

Uses

Treatment
Closure of patent ductus arteriosus (PDA): Long-term outcomes are not improved when preterm infants, younger than 14 days, are treated routinely for patent ductus arteriosus. Treatment benefits when administered after 2 weeks of age or in high-risk infants in the first 2 postnatal weeks are unknown [8]. There are risks to NSAIDs and there is a high rate of spontaneous closure; therefore, treatment should be limited to select preterm newborns with symptomatic PDA [9][10]. At 36 weeks' postmenstrual age, there was no significant difference in mortality or moderate to severe bronchopulmonary dysplasia between NSAID treatment (initiated 2 to 28 days postnatally) and no treatment in a cohort of 12,018 preterm infants (gestational age 28 weeks or younger) with patent ductus arteriosus [11].
Ibuprofen vs Indomethacin: PDA closure rates were similar for IV or oral ibuprofen and IV or oral indomethacin (RR 1.07, 95% CI 0.92 to 1.24) in a meta-analysis of 39 studies of

preterm and/or low birth weight infants (N=2843 infants); however, ibuprofen was associated with a reduced duration of ventilator support (mean difference -2.35 days, 95% CI -3.71 to -0.99) and reduced risk of necrotizing enterocolitis (NEC; RR 0.68, 95% CI 0.49 to 0.94), and oliguria (RR 0.28, 95% CI 0.14 to 0.54). Serum/plasma creatinine levels 72 hours post-treatment were significantly lower in the ibuprofen group (mean difference -8.12 micromol/L, 95% CI -10.81 to -5.43) but there was high heterogeneity between studies and the GRADE level of evidence was low. PDA closure rates were also similar for oral ibuprofen only compared with IV or oral indomethacin (RR 0.96, 95% CI 0.73 to 1.27) and the risk of NEC was decreased in patients receiving ibuprofen (RR 0.41, 95% CI 0.23 to 0.73) [12].

Acetaminophen vs Ibuprofen vs Indomethacin: Acetaminophen IV is as effective as indomethacin IV and ibuprofen (at standard doses) IV in the closure of PDA in preterm infants (gestational age less than 28 weeks) with hemodynamically significant PDA in a randomized study (n=300). After the first treatment course, the closure rates were 80%, 77%, and 81% for acetaminophen, ibuprofen, and indomethacin, respectively. Adverse effects (increase in serum creatinine and serum BUN and decrease in platelet count and urine output) were significantly more with ibuprofen and indomethacin than acetaminophen. Bilirubin significantly increased with ibuprofen. The mean weights were 1.1 kg, 1 kg, and 1.1 kg in the infants treated with acetaminophen, ibuprofen, and indomethacin, respectively [13].

Infusing indomethacin over a prolonged period may reduce the vasoconstriction and subsequent detrimental effect on the end organs (renal, GIT, and CNS). Infants (n=63) randomized to 36-hour continuous IV infusion of indomethacin 17 mcg/kg/hr (27.8 weeks gestational age, 1100 g birth weight) compared with ibuprofen lysine (27.8 weeks gestational age, 1060 g birth weight) experienced no apparent differences in renal function or renal, mesenteric, or cerebral blood flow (by Doppler measurement); furthermore, PDA closed in 74% vs 59% (p=0.132), respectively [14]. However, the manufacturer recommends against further dilution after reconstitution of the lyophilized powder and the stability and sterility of preservative-free indomethacin are unknown [1].

Prophylaxis

Prevention of patent ductus arteriosus (PDA): There are risks to indomethacin and there is a high rate of spontaneous closure (up to 60%); therefore, prophylaxis (in the first 24 hours of life) with indomethacin is not recommended for all preterm infants [9][10], particularly, indomethacin may not be justified for perceived benefits on PDA or an expectation of better long-term outcomes [8].

Prevention of intraventricular hemorrhage (IVH): In settings of high IVH rates, prophylactic indomethacin may be appropriate. Similarly, prophylactic indomethacin may be appropriate if early, severe pulmonary hemorrhage is common. However, indomethacin may not be justified for perceived benefits on PDA or an expectation of better long-term outcomes [8]. A meta-analysis (n=2872; 19 trials) demonstrated short-term benefits including a reduction in frequency of severe intraventricular hemorrhage, the incidence of symptomatic PDA, and surgical ligation of the PDA in preterm infants administered prophylactic indomethacin on the first day after birth. However, long-term benefit on death or neurodevelopment at 18 to 36 months corrected age was not demonstrated [2][15]. Oliguria/anuria occurred more often in infants on prophylactic indomethacin, but any renal impairment was temporary [2]. Routine use of prophylactic indomethacin has been questioned [16][17].

Pediatric FDA Approved Indications: IV indomethacin is indicated to close a hemodynamically significant patent ductus arteriosus in premature infants weighing between

500 to 1750 g [1].

Administration

Infuse the 0.5 to 1 mg/mL solution over 20 to 30 minutes [1].

MEDICATION SAFETY

Contraindications/Precautions

Contraindicated in active bleeding, significant thrombocytopenia or coagulation defects, necrotizing enterocolitis, untreated proven or suspected infection, and/or significantly impaired renal function [1].

Precautions
If oliguria occurs, observe for hyponatremia and hypokalemia, and consider prolonging the dosing interval of renally excreted drugs (eg, gentamicin). Consider withholding feedings. Concomitant therapy with furosemide may lead to increased hyponatremia and a significant rise in serum creatinine [20][21].

Adverse Effects

Hypoglycemia is common, usually preventable by increasing the glucose infusion rate by 2 mg/kg per minute. Causes **platelet dysfunction**. Rapid (less than 5-minute) infusions are associated with **reductions in organ blood flow**. **Gastrointestinal perforations** occur frequently if used concurrently with corticosteroids.
Renal Effects: Urine output decreased significantly more in indomethacin-treated (41%) compared with ibuprofen-treated (21%) preterm neonates (mean gestational age, 26 weeks; birth weight, less than 1000 g) with clinically significant patent ductus arteriosus (PDA) in a randomized double-blind study (n=144). The difference was significant for day 1, but not days 3, 5, 7, or 14. There was also a significantly greater increase in serum creatinine and decrease in GFR for the first 2 days with indomethacin. Dosages used were ibuprofen lysine 10 mg/kg IV for 1 dose, then 5 mg/kg/dose every 24 hours for 2 doses and indomethacin 0.2 mg/kg IV for 1 dose, then 0.1 mg/kg/dose every 24 hours for 2 doses [22].

Black Box Warning

NSAIDs cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment

and may increase with duration of use. Indomethacin is contraindicated in the setting of CABG surgery. NSAIDs can also cause an increased risk of serious gastrointestinal (GI) adverse events, including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at a greater risk for serious GI events [18][19].

Solution Compatibility

Sterile water for injection.
(No visual precipitation in 24 hours): $D_{2.5}W$, D_5W, and NS.

Solution Incompatibility

$D_{7.5}W$, and $D_{10}W$

Terminal Injection Site Compatibility

Furosemide, insulin, nitroprusside, potassium chloride, and sodium bicarbonate.

Terminal Injection Site Incompatibility

Calcium gluconate, cimetidine, dobutamine, dopamine, gentamicin, and tobramycin.

Monitoring

Monitor urine output, serum electrolytes, glucose, creatinine and BUN, and platelet counts. Assess murmur, pulse pressure. Assess for gastrointestinal bleeding by gastric and fecal occult blood testing. Observe for prolonged bleeding from puncture sites.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action: Indomethacin is a nonsteroidal anti-inflammatory drug that has an unknown mechanism of action. However, the drug exerts antiinflammatory, analgesic, and antipyretic effects by inhibiting the synthesis of prostaglandin. Decreases cerebral, renal, and gastrointestinal blood flow.

Metabolized in the liver to inactive compounds and excreted in the urine and feces. Serum half-life is approximately 30 hours, with a range of 15 to 50 hours, partially dependent on postnatal age. In most studies, the response of the ductus and adverse effects of indomethacin are only weakly correlated with plasma concentration.

ABOUT

Special Considerations/Preparation

Supplied: Lyophilized powder in 1-mg single-dose vials [1].
Indomethacin sodium trihydrate salt is not buffered, and is insoluble in solutions with pH less than 6; the manufacturer therefore recommends against continuous infusion in typical IV solutions. Reconstitute using 1 to 2 mL of preservative-free NS or sterile water for injection.

Stability: Indomethacin sodium trihydrate 0.5 mg/mL (reconstituted with sterile water) was stable for 14 days in polypropylene syringes at 2 to 6 degrees C and at 21 to 25 degrees C. Reconstituted indomethacin was stable in its original glass vial for 14 days when stored at 2 to 6 degrees C, and for 12 days when stored at 21 to 25 degrees C [23].

DOSING/ADMINISTRATION

Dose

Intravenous: Infuvite® Pediatric is a sterile product consisting of two vials: a 4 mL vial labeled **Vial 1** and a 1 mL vial labeled **Vial 2**. The daily dose is a function of infant weight as indicated in the following table [1].
Do not exceed this daily dose.

Infuvite Dosing			
	less than 1 kg *	**1 kg to less than 3 kg ***	**3 kg or more; up to 11 years of age**
Vial 1	1.2 mL	2.6 mL	4 mL
Vial 2	0.3 mL	0.65 mL	1 mL
*** supplemental vitamin A may be required for low-birth weight infants.**			

Uses

Pediatric FDA Approved Indications
Multivitamin maintenance dosage for infants and children up to 11 years of age receiving parenteral nutrition or in patients in "stress situations" where administration by the IV route is necessary (eg, surgery, extensive burns, fractures and other trauma, severe infectious diseases, and comatose states) to prevent tissue depletion of nutrients [1].

Administration

Should not be given as a direct, undiluted intravenous injection.

Add the required dose to not less than 100 mL of dextrose, saline, or similar infusion solutions [1].

MEDICATION SAFETY

Contraindications/Precautions

Contraindicated in patients with preexisting hypervitaminosis [1].

Product contains aluminum; risk of **aluminum toxicity** with prolonged administration in the presence of renal impairment in preterm neonates [1].
Vitamin K in Infuvite may antagonize the hypoprothrombinemic response of anticoagulant drugs [1].
E-Ferol syndrome is associated with polysorbates, which is included in Infuvite [1].

Adverse Effects

Infuvite® Pediatric is administered in intravenous solutions, which may contain aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired [1]. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solution, which contain aluminum.
Research indicates that patients with impaired kidney function, including premature neonates who receive parenteral levels of aluminum at greater than 4 to 5 mcg/kg per day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration [1].

Anaphylactic reactions following parenteral multivitamin administration have been reported rarely [1].

Solution Compatibility

D_5W, $D_{10}W$, NS, D_5NS

Terminal Injection Site Incompatibility

Alkaline solutions or moderately alkaline drugs (acetazolamide, aminophylline, chlorothiazide, and sodium bicarbonate), ampicillin, tetracycline.
Direct addition to intravenous fat emulsions is not recommended [1].

Monitoring

Assess blood vitamin concentrations periodically, particularly in patients on long-term therapy

to monitor for vitamin deficiencies or excesses [1].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

See table below for nutrient amounts [1].

INFUVITE® Pediatric	
Vial 1 (4 mL)	**Amount**
Vitamin A* (as palmitate)	2300 international units (0.7 mg)
Vitamin D* (cholecalciferol)	400 international units (10 mcg)
Ascorbic Acid (vitamin C)	80 mg
Vitamin E* (dl-alpha-tocopheryl acetate)	7 international units (7 mg)
Thiamine (as hydrochloride) B 1	1.2 mg
Riboflavin (as phosphate) B 2	1.4 mg
Niacinamide B 3	17 mg
Pyridoxine hydrochloride B 6	1 mg
Dexpanthenol (d-Panthenol)	5 mg
Vitamin K 1 *	0.2 mg
Vial 2 (1 mL)	
Biotin	20 mcg
Folic Acid	140 mcg
Vitamin B 12 (cyanocobalamin)	1 mcg
* Polysorbate 80 is used to water solubilize the oil-soluble vitamins A, D, E, and K.	
Vial 1 (4 mL) Inactive ingredients: 50 mg polysorbate 80, sodium hydroxide and/or hydrochloric acid for pH adjustment and water for injection.	
Vial 2 (1 mL) Inactive ingredients: 75 mg mannitol, citric acid and/or sodium citrate for pH adjustment and water for injection.	
Combination of Vial 1 and 2 contains no more than 30 mcg/L of aluminum.	

ABOUT

Special Considerations/Preparation

After Infuvite® Pediatric is diluted in an intravenous infusion, the resulting solution is ready for immediate use. Inspect visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Exposure to light should be minimized. Discard any unused portion. **Store between 2 and 8 degrees C (36 and 46 degrees F). Contains no more than 30 mcg/L of aluminum (vials 1 and 2 combined)**[1].

Insulin Human Regular

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Neonatal diabetes mellitus
Continuous subQ infusion (pump therapy): In published case reports, the total daily dose of insulin in infants receiving pump therapy used ranged from 0.15 to 1 units/kg/day, with basal rates of 0.14 to 0.7 units/kg/day or 0.01 to 0.15 units/hr [1]

Hyperglycemia
Continuous IV infusion: 0.01 to 0.1 unit/kg/hour (Beardsall 2008, Ditzenberger 1999, Simeon 1994).
Titrate using blood glucose concentration/reagent strips.

Hyperkalemia
Initial: Regular insulin 0.1 to 0.2 units/kg/hour in combination with 0.5 g/kg/hour of dextrose given as continuous IV infusion. Insulin and dextrose dosages are adjusted based on serum glucose and potassium concentrations.

Uses

Neonatal diabetes mellitus: Several case reports on continuous subQ insulin infusion (pump therapy) in neonates have been reported on several different types of insulins (human regular, lispro, aspart). In the first report, an infant girl was switched from multiple injections a day to pump therapy with continuous glucose monitoring (CGM) at 21 days of age after 7 days of IV therapy. She was discharged home with a basal dose of 0.6 units/kg/day plus mealtime boluses of 0.2 units/kg/day. The patient's blood glucose was fairly stable through followup (at 35 months; 4.6 to 9.1 mmol/L) with only rare episodes of hypoglycemia [1]. In the second report, an infant boy with homozygous PTF1A enhancer mutation was switched to pump therapy at 1 month due to wide fluctuations of blood glucose while using NPH/rapid-acting insulin for glycemic control. Despite this switch, HbA1c was still 10.5% at last follow up (1.4 years) and frequent hypoglycemic events occurred. The investigators suggest that this may be due to glucagon deficiency due to pancreatic agenesis. The patient was receiving 0.69 units/kg/day with pump therapy, along with pancreatic enzymes and supplementation of fat soluble vitamins [10].
Pump therapy may be helpful in management on neonatal diabetes mellitus due to its capability to deliver small doses of insulin, allows for small dose changes with meals, and enables temporary basal rates and square-wave boluses to be set for infants who eat slowly or take frequent small feeds [1].

Very Low Birth Weight **Hyperglycemic infants with persistent glucose intolerance**.

Hyperglycemia in critically ill: Tight glycemic control (72 to 126 mg/dL) compared with conventional glycemic control (less than 216 mg/dL) did not provide improved number of days alive or mechanical ventilation rate at day 30 in critically ill patients (n=1369, newborns (36 weeks gestation or more) to 16 years of age non-diabetic children) on mechanical ventilation and vasoactive drugs. Furthermore, severe hypoglycemic episodes were more common in the tight glycemic control group (7.3% vs 1.5%, p less than 0.001) [11].

Hyperkalemia in combination with dextrose.

Pediatric FDA Approved Indications
Regular human insulin is indicated for diabetes mellitus; type 1 and type 2 in pediatric patients (HumuLIN® R)[3] and type 1 in pediatric patients 2 to 18 years of age [2]. HumuLIN® R U-500 is indicated to improve glycemic control in patients with diabetes mellitus requiring more than 200 units of insulin daily [12][13].

Administration

Intravenous
• Only regular insulin for injection may be administered intravenously. For continuous infusion, dilute **regular insulin** in compatible solution to a concentration of 0.05 to 1 unit/mL in polypropylene infusion bags (NovoLIN R)[2] and 0.1 to 1 unit/mL in polyvinyl chloride bags (HumuLIN R)[3]. The recommended standard neonate concentrations are 0.1 unit/mL and 0.5 unit/mL [4].
• **Tubing:** To saturate plastic tubing binding sites, fill IV tubing with insulin solution and wait for at least 20 minutes before infusing (preconditioning). The use of higher insulin concentrations and longer wait times will shorten the time to steady-state [5][6][7]. Other studies have examined preconditioning and/or priming volumes; running a certain volume of insulin infusion through the tubing prior to initiation [5][7]. One study demonstrated that 20 mL of priming volume was sufficient to minimize adsorption losses for a 1 unit/mL insulin infusion [8]. Results show that pre-flushing IV administration sets leads to greater and more predictable insulin delivery over time [5][9][7] and that the combination of preconditioning and flushing offers the best combination to reduce insulin adsorption [5][7].

MEDICATION SAFETY

Contraindications/Precautions

Contraindications
During episode of hypoglycemia [14][12]
Hypersensitivity to human regular insulin or any of its components [14][12]

Precautions
Administration: Do not administer 500 units/mL concentration IV, IM, or via insulin pump; do not dilute or mix with any other insulin products or solutions [12]

Administration: Pen devices and syringes are for single patient use only and never to be shared, even if the needle is changed, due to increased risk for transmission of bloodborne pathogens [14][12]
Concomitant use: Concomitant peroxisome proliferator-activated receptor (PPAR)-gamma agonist therapy may cause dose-related fluid retention, potentially leading to new or worsening heart failure; monitoring recommended and dose reduction or discontinuation of PPAR-gamma agonist therapy may be required if heart failure develops [14][12]
Endocrine and metabolic: Hyperglycemia or hypoglycemia may occur with changes in insulin regimen; increased glucose monitoring recommended [14][12]
Endocrine and metabolic: Severe hypoglycemia may occur 18 to 24 hours after administration with 500 units/mL [12]
Endocrine and metabolic: Symptomatic hypoglycemia may be difficult to recognize in patients with longstanding diabetes, patients with nerve disease, patients using medications that block the sympathetic nervous system (eg, beta blocker) or patients who experience recurrent hypoglycemia; increased glucose monitoring recommended [14][12]
Endocrine and metabolic: Increased risk for hypoglycemia with injection site changes, changes in meal patters, changes in level of physical activity, changes to coadministered medication, and patients with renal or hepatic impairment; increased glucose monitoring recommended [15][14][12]
Endocrine and metabolic: Increased risk of hyperglycemia with repeated injections into areas of lipodystrophy or localized cutaneous amyloidosis [15]
Endocrine and metabolic: Hypokalemia may occur; monitoring recommended in patients at risk for hypokalemia (eg, patients using potassium-lowering medications, patients taking medications sensitive to serum potassium) [14][12]
Hepatic: Patients with hepatic impairment may require more frequent dose adjustments [14][12]
Immunologic: Severe, life-threatening, generalized allergy, including anaphylaxis, have been reported; discontinue if reactions occur [14][12]
Medication errors: Hyperglycemia, hypoglycemia, and death have been reported due to medication error with 500 units/mL; ensure correct insulin is being used [12]
Renal: Patients with renal impairment may require more frequent dose adjustments [14][12]

Adverse Effects

May rapidly induce hypoglycemia. Insulin resistance may develop, causing a larger dose requirement. Euglycemic hyperinsulinemia due to exogenous insulin administration may cause metabolic acidosis.
The most recent randomized controlled trial (Beardsall) and systematic review (Raney) concluded that routine use of insulin in VLBW infants to promote growth is not warranted.

Monitoring

Follow blood glucose concentration frequently (every 15 to 30 minutes) after starting insulin infusion and after changes in infusion rate. Monitor potassium concentrations closely when treating hyperkalemia.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Degraded in liver and kidney. Enhances cellular uptake of glucose, conversion of glucose to glycogen, amino acid uptake by muscle tissue, synthesis of fat, and cellular uptake of potassium. Inhibits lipolysis and conversion of protein to glucose. Plasma half-life in adults is 9 minutes.

ABOUT

Special Considerations/Preparation

Available: Regular human insulin [rDNA origin] is available as a 100-unit/mL concentration in 10-mL vials.
Dilution: For subcutaneous administration, dilute with sterile water or NS to a concentration of 0.5 or 1 unit/mL. For IV administration, make a 10 units/mL dilution with sterile water, then further dilute in compatible solution to a concentration of 0.05 to 1 unit/mL. **Keep refrigerated.**
KwikPen(R)
Storage (unopened): Store unopened pens under refrigerated conditions between 2 and 8 degrees C (36 and 46 degrees F) until expiration date, or at room temperature below 30 degrees C (86 degrees F) for up to 28 days; protect from heat, light, and freezing.[16]
Storage (opened): Store opened pens at room temperature below 30 degrees C (86 degrees F) for up to 28 days; discard unused portion. Do not refrigerate. [17]
Vials
Storage (unopened): Store unopened vials under refrigerated conditions between 2 and 8 degrees C (36 and 46 degrees F) until expiration date, or at room temperature below 30 degrees C (86 degrees F) for up to 40 days; protect from heat, light, and freezing.[16]
Storage (opened): Store unopened vials under refrigerated conditions between 2 and 8 degrees C (36 and 46 degrees F) for up to 40 days, or at room temperature below 30 degrees C (86 degrees F) for up to 40 days; do not freeze, discard unused portion.[16]

Ipratropium

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Administer every 6 to 8 hours as a metered dose inhaler (MDI) or nebulized solution. Doses studied in intubated neonates range from 2 puffs (34 mcg) to 4 puffs (68 mcg) via MDI with spacer device placed in the inspiratory limb of the ventilator circuit, and 75 to 175 mcg via jet nebulizer. Simulated neonatal lung models suggest greater delivery when using a spacer with the MDI. Use chlorofluorocarbon free preparations when administering to neonates.

Optimal dose in neonates has yet to be determined due to differences in aerosol drug delivery techniques, although the therapeutic margin appears to be wide.

Uses

Anticholinergic bronchodilator for primary treatment of chronic obstructive pulmonary diseases and adjunctive treatment of acute bronchospasm. Ipratropium is not useful in the treatment of bronchiolitis.

MEDICATION SAFETY

Adverse Effects

Temporary blurring of vision, precipitation of narrow-angle glaucoma, or eye pain may occur if solution comes into direct contact with the eyes.

Monitoring

Assess degree of bronchospasm.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Ipratropium bromide is a quaternary ammonium derivative of atropine. It produces primarily large airway bronchodilation by antagonizing the action of acetylcholine at its receptor site. It is relatively bronchospecific when administered by inhalation because of limited absorption through lung tissue. Peak effect occurs 1 to 2 hours after administration. Duration of effect is 4 to 6 hours in children. The combination of ipratropium with a beta-agonist produces more bronchodilation than either drug individually.

ABOUT

Special Considerations/Preparation

Metered-dose inhaler: Atrovent® HFA is available in a pressurized metered-dose aerosol unit (contains no chlorofluorocarbons (CFC)) providing 200 actuations per each 12.9-g canister. Each actuation delivers 21 mcg of ipratropium from the valve and 17 mcg from the mouthpiece.

Solution for inhalation: Supplied in 2.5-mL vials, containing ipratropium bromide 0.02% (200 mcg/mL) in a sterile, preservative-free, isotonic saline solution that is pH-adjusted to 3.4 with hydrochloric acid. It may be mixed with albuterol or metaproterenol if used within 1 hour. Store at room temperature in foil pouch provided. Protect from light.

Iron Dextran

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

0.4 to 1 mg/kg (400 to 1000 mcg/kg) per day IV continuous infusion .

Uses

Iron supplementation in patients unable to tolerate oral iron, especially those also being treated with erythropoietin.

Administration

For continuous infusion, iron dextran may be added to peripheral nutrition solutions. The solution must contain an amino acid final concentration of at least 2% [1].

MEDICATION SAFETY

Adverse Effects

No adverse effects have been observed in patients who have received low doses infused continuously. Large (50-mg) intramuscular doses administered to infants were associated with increased risk of infection. Retrospective reviews of adult patients who received larger doses injected over a few minutes report a 0.7% risk of immediate serious allergic reactions, and a 5% risk of delayed such as myalgia, arthralgia, phlebitis, and lymphadenopathy.

Black Box Warning

Anaphylactic-type reactions, including fatalities, have followed parenteral administration. Resuscitation equipment and trained personnel must be readily available during iron dextran administration. **Must perform test dose.** Observe for signs/symptoms of anaphylactic-type reactions. Fatal reactions have occurred following the test dose and have occurred in situations where the test dose was tolerated. Patients with a history of drug allergy or

multiple drug allergies may be at increased risk of anaphylactic-type reactions.

Monitoring

Periodic CBC and reticulocyte count. Observe Dex/AA solution for rust-colored precipitates..

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Iron dextran for intravenous use is a complex of ferric hydroxide and low molecular mass dextran. The dextran serves as a protective lipophilic colloid. Radiolabeled iron dextran injected into adult subjects localized to the liver and spleen before being incorporated into RBC hemoglobin. Complete clearance occurred by 3 days. Approximately 40% of the labeled iron was bound to transferrin within 11 hours. The addition of iron dextran to Dex/AA solutions inhibits the spontaneous generation of peroxides..

ABOUT

Special Considerations/Preparation

Available as a 50 mg/mL concentration in 2-mL single-dose vials. Store at room temperature. **Iron dextran products are not interchangeable**[2].

Isoproterenol

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

0.05 to 0.5 mcg/kg/minute continuous IV infusion.
Maximum dose 2 mcg/kg per minute.
Dosage often titrated according to heart rate.
Acidosis should be corrected before infusion.

Uses

Increases cardiac output in patients with cardiovascular shock. Pulmonary vasodilator (older infants).

Administration

Solution Preparation Calculations

Maximum concentration 20 mcg/mL. Concentrations as low as 2 mcg/mL has been used in adults [1]

To calculate the AMOUNT of drug needed per defined final fluid volume:
Desired final concentration (mg/mL) x defined final fluid volume (mL) = AMOUNT of drug to add to final infusion solution (mg).

To calculate the VOLUME of drug needed per defined final fluid volume:
*AMOUNT of drug to add (mg) ÷ drug (vial) concentration (mg/mL) = VOLUME of drug to add (mL)

Example (for Isoproterenol): Mix 50 mL of 10 mcg/mL solution using isoproterenol concentration of 0.2 mg/mL.
10 mcg/mL = 0.01 mg/mL
0.01 mg/mL x 50 mL = 0.5 mg isoproterenol
***0.5 mg ÷ 0.2 mg/mL = 2.5 mL of isoproterenol**

Add 2.5 mL of isoproterenol (0.2 mg/mL) to 47.5 mL of compatible solution (eg, D_5W) to yield 50 mL of infusion solution with a concentration of 10 mcg/mL.

Isoproterenol Titration Chart		
Concentration (mcg/mL)	**Dose (mcg/kg/min)**	**IV Rate (mL/kg/hour)**
5	0.05 0.1 0.5 1	0.6 1.2 6 12
10	0.05 0.1 0.5 1	0.3 0.6 3 6
15	0.05 0.1 0.5 1	0.2 0.4 2 4
20	0.05 0.1 0.5 1	0.15 0.3 1.5 3

MEDICATION SAFETY

Adverse Effects

Cardiac arrhythmias. Tachycardia severe enough to cause CHF. Decreases venous return to heart. Systemic vasodilation. May cause hypoxemia by increasing intrapulmonary shunt. Hypoglycemia.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Amiodarone, caffeine citrate, calcium chloride, calcium gluceptate, cimetidine, dobutamine, famotidine, heparin, hydrocortisone succinate, milrinone, netilmicin, nitroprusside, pancuronium bromide, potassium chloride, propofol, ranitidine, remifentanil, and vecuronium.

Terminal Injection Site Incompatibility

Furosemide and sodium bicarbonate.

Monitoring

Continuous vital signs, intra-arterial blood pressure, CVP monitoring preferable. Periodic blood glucose reagent strips.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

β-receptor stimulant, sympathomimetic. Increases cardiac output by 1) increasing rate (major) and 2) increasing strength of contractions (minor). Insulin secretion is stimulated. Afterload reduction via β_2 effects on arterioles.

ABOUT

Special Considerations/Preparation

Supplied as 0.2 mg/mL solution in 1-mL and 5-mL ampuls.

DOSING/ADMINISTRATION

Dose

Screen for Hepatitis B virus prior to initiating therapy [1].
HIV Infection, Treatment and Perinatal Prophylaxis:
32 weeks' gestation or more:
Birth to 4 weeks' postnatal age: 2 mg/kg/dose orally every 12 hours [1].

Dose Adjustments
Renal Impairment: Although there are no dosing recommendations available for neonates or pediatric patients with renal impairment, a reduction in the dose and/or an increase in the dosing interval should be considered [2].

Uses

Antiretroviral Management in the Newborn: Lamivudine plus abacavir or zidovudine is a preferred dual-NRTI combination in treatment regimens for HIV infection in newborn patients to less than 1 month. Lamivudine and zidovudine plus nevirapine or raltegravir is the preferred initial therapy regimen for newborns at high risk for perinatal HIV transmission [1]

Risk of HIV in Newborn	Description	Antiretroviral (ARV) Management †
Low risk of transmission	Infants 37 weeks or older gestation when the mother: • is currently receiving or has received 10 consecutive weeks of ART during pregnancy, and • has achieved and maintained or maintained viral suppression (2 consecutive tests with HIV RNA levels less than 50 copies/mL obtained at least 4 weeks apart) for	Zidovudine for 2 weeks (footnote 1)

	the duration of pregnancy, and • has HIV RNA <50 copies/mL at or after 36 weeks and within 4 weeks of delivery, and • did not have acute HIV infection during pregnancy, and • has reported good ART adherence, and adherence concerns have not been identified	
	•Infants born to mothers who do not meet the criteria above but who have HIV RNA <50 copies/mL at or after 36 weeks gestation	Zidovudine for 4 to 6 weeks (footnote 1)
	Premature infants (<37 weeks gestation) who are not at high risk of perinatal acquisition of HIV	
Higher risk of transmission	•Mother has not received antepartum or intrapartum ARV therapy, or •Mother has received only intrapartum ARV therapy, or •Mother has received antepartum and intrapartum ARV drugs but does not have viral suppression within 4 weeks prior to delivery, or •Mother has acute or primary HIV	Zidovudine, lamivudine, and nevirapine for 2 to 6 weeks; if duration of the 3-drug regimen is shorter than 6 weeks, zidovudine should be continued to complete 6 weeks of prophylaxis (footnote 3)
		Zidovudine, lamivudine, and raltegravir for 2 to 6 weeks; if

	infection during pregnancy or breastfeeding (footnote 2)	duration of the 3-drug regimen is shorter than 6 weeks, zidovudine should be continued to complete 6 weeks of prophylaxis (footnote 3)
Presumed exposure	•Mother with unknown HIV status who test positive at delivery or postpartum, or whose newborn has positive HIV antibody test	•ARV management is the same as those with higher risk of transmission (see above). •Discontinue immediately if supplemental testing confirms mother does not have HIV.
Confirmed (footnote 4)	•Confirmed positive newborn HIV virologic test/nucleic acid test	Three-drug ARV regimen using treatment doses. The preferred regimen in newborns is 2 NRTIs plus nevirapine or raltegravir
Footnotes: 1. Zidovudine prophylaxis is recommended for infants born to mothers with HIV-2 mono-infection. If mother has HIV-1 and HIV-2 co-infection, the ARV regimen should be determined based on risk. Raltegravir should be considered in patients at high risk of perinatal HIV-2 acquisition because HIV-2 is not susceptible to nevirapine 2. Most panel members opt to administer presumptive HIV therapy to infants born to mother with acute HIV infection due to the higher risk of in utero transmission. If acute HIV is diagnosed during breastfeeding, the mother should immediately discontinue breast feeding 3. The optimal duration of presumptive HIV therapy in newborns with high risk for HIV acquisition is unknown. Patients should receive the zidovudine portion of the three-drug regimen for 6 weeks. The other two ARVs		

(emtricitabine/nevirapine or emtricitabine/raltegravir may be administered for 2 to 6 weeks. The recommended duration of treatment with the three-drug regimen varies depends on HIV NAT results, maternal viral load at time of delivery, and additional risk factors for HIV transmission including breastfeeding 4. ART should be initiated without waiting for results of confirmatory HIV NAT testing. However, the specimen for confirmatory testing should be attained prior to ART initiation
Reference: https://clinicalinfo.hiv.gov /en/guidelines/pediatric-arv/whats-new April 2022

Antiretroviral Regimens for Initial Therapy	
Age Range	Regimen
Preferred Regimens	
Birth to less than 14 days (footnote 1, 2)	Any weight: 2 NRTIs plus nevirapine
	2 kg or more: 2 NRTIs plus raltegravir (footnote 3)
14 days (and 2 kg or greater) to less than 4 weeks	2 NRTIs plus lopinavir/ritonavir (footnote 2)
	2 NRTIs plus raltegravir (footnote 3)
4 weeks or older (and 3 kg or greater) to less than 2 years	2 NRTIs plus dolutegravir (footnote 4)
2 years (and 14 kg or greater) or older	2 NRTIs plus bictegravir (footnote 5)
Alternative Regimens	
14 days to less than 3 years	2 NRTIs plus nevirapine (footnote 7)
4 weeks to less than 3 months	Any weight: 2 NRTIs plus lopinavir/ritonavir (footnote 2)
	2 kg or more: 2 NRTIs plus raltegravir (footnote 3)
3 months to less than 3 years	2 NRTIs plus atazanavir/ritonavir
	2 NRTIs plus lopinavir/ritonavir (footnote 2)

	2 NRTIs plus raltegravir (footnote 3)	
3 years or older	2 NRTIs plus atazanavir/ritonavir	
	2 NRTIs plus darunavir/ritonavir (footnote 8)	
	2 NRTIs plus efavirenz (footnote 9)	
	2 NRTIs plus lopinavir/ritonavir (footnote 2)	
	25 kg or more	2 NRTIs plus elvitegravir/cobicistat (footnote 10)
	35 kg or more	2 NRTIs plus doravirine (footnote 11)
12 years or older with SMR 1 to 3	2 NRTIs plus one of the following: atazanavir/ritonavir, darunavir/ritonavir, efavirenz, lopinavir/ritonavir, raltegravir	
	25 kg or more	2 NRTIs plus elvitegravir/cobicistat
	35 kg or more	2 NRTIs plus one of the following: doravirine (footnote 11), rilpivirine (footnote 12), atazanavir/cobicistat
	40 kg or more	2 NRTIs plus darunavir/cobicistat
Preferred Dual NRTI Options for Use with Additional Drugs		
Birth to 1 month	abacavir plus lamivudine or emtricitabine (footnote 6)	
	zidovudine plus lamivudine or emtricitabine	
1 month to less than 2 years	abacavir plus lamivudine or emtricitabine (footnote 6)	
2 years or older and SMR 1 to 3	abacavir plus lamivudine or emtricitabine(footnote 6)	
	14 kg or greater and receiving a regimen that contains an INSTI or a NNRTI	emtricitabine/tenofovir alafenamide
	35 kg or greater and	

	receiving a regiment that contains a boosted PI	

Alternative Dual NRTI Options for Use with Additional Drugs	
1 month to less than 6 years	zidovudine plus abacavir (footnote 6)
	zidovudine plus lamivudine or emtricitabine
2 years to 12 years	tenofovir disoproxil fumarate plus lamivudine or emtricitabine
6 years or older and SMR 1 to 3	zidovudine plus abacavir (footnote 6)
	zidovudine plus lamivudine or emtricitabine

Footnotes:
1. Available clinical trial data do not suggest that initiating treatment within the first 14 days of life lead to better clinical outcomes than initiation after 14 days of age. Consult an expert in pediatric HIV infection before initiating in infants less than 14 days.
2. In general, lopinavir/ritonavir should not be administered to neonates before a postmenstrual age of 42 weeks and a postnatal age of 14 days or more.
3. Raltegravir film-coated tablets or chewable tablets can be used in children at least 2 years old. Consider use of the granules in infants from birth to 2 years. No dose recommendations are available for preterm infants or infants weighing less than 2 kg at birth.
4. Dolutegravir dispersible tablets can be administered in patients 4 weeks or older and 3 kg or greater. Dolutegravir film-coated tablets can be used in patients 14 kg or greater.
5. Only available as part of a fixed-dose combination tablet that contains bictegravir/emtricitabine/tenofovir alafenamide.
6. Abacavir is not approved by the FDA for use in full-term neonates and infants less than 3 months. Recent trial data from the IMPAACT P1106 trial and 2 observational cohorts provides reassurance on the safety of abacavir in patients less than 3 months. Before abacavir administration, a negative HLA-B 5701 allele test should be established
7. Do not use nevirapine in postpubertal girls if CD4 count is greater than 250/mm(3) unless

clear benefit. Nevirapine is FDA-approved for infants 15 days or older.8. Darunavir should only be used in children 10 kg or more. Do not use darunavir once daily in children younger than 12 years or weighing less than 40 kg or if any one of the following resistance-associated substitutions are present: V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, and L89V. 8. Darunavir/ritonavir-boosted is an alternative recommendation for children 6 years to younger than 12 years and weighing greater than 25 kg because there are options that can be administered once-daily and that are better tolerated. Darunavir/ritonavir-boosted administered once daily is an option for adolescents 12 years or older and weighing at least 40 kg who are not sexually mature (SMR 1 to 3) 9. Efavirenz is not recommended as initial therapy for children 3 months to 3 years (weighing at least 3.5 kg), even though it's FDA approved for this age group. Available as part of fixed-dose combination tablets 10. Elvitegravir is currently recommended only in fixed-dose combination tablets. Tablets containing elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide are an alternative for children weighing at least 25 kg due to multiple drug-drug interactions with cobicistat and a lower barrier to the development of resistance to elvitegravir 11. Doravirine is not FDA approved for pediatric use. Based on data on the efficacy and tolerability of doravirine in adults, as well as early findings from PK studies, the Panel recommends doravirine as an alternative treatment option for patients 35 kg or more 12. Rilpivirine should only be administered to adolescents 12 years or older and weighing 35 kg or more who have an initial viral load of 100,000 copies/mL or less. Available as part of a fixed-dose combination products.
INSTIs: bictegravir, dolutegravir, elvitegravir, raltegravir
NRTIs: abacavir, emtricitabine, lamivudine, tenofovir alafenamide, tenofovir disoproxil fumarate, zidovudine
NNRTIs: doravirine, efavirenz, nevirapine, rilpivirine
PIs: atazanavir, darunavir, lopinavir, ritonavir
Key: INSTI = integrase strand transfer inhibitor, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase

inhibitor, PI = protease inhibitor, SMR = sexual maturity rating
Reference: https://clinicalinfo.hiv.gov /en/guidelines/pediatric-arv/whats-new April 2022

Prevention of maternal-fetal HIV transmission: In a phase III randomized trial (n=1684), the combination of 6 weeks of zidovudine plus 3 doses of nevirapine or the combination of 6 weeks of zidovudine plus nelfinavir and lamiVUDine for 2 weeks was associated with a lower intrapartum transmission rate when compared with zidovudine alone in infants born to women who received no antenatal antiretroviral therapy (2.2% versus 2.5% versus 4.9%, respectively). The zidovudine/nelfinavir/lamiVUDine regimen was associated with increased toxicity (eg, neutropenia) [3].

Pediatric FDA Approved Indications
Epivir®
Treatment of HIV-1 infection in combination with other antiretroviral agents in children 3 months of age and older [2].

Administration

Can be given without regard to meals [2].

MEDICATION SAFETY

Contraindications/Precautions

Dual-NRTI therapy with emtricitabine and lamiVUDine is NOT recommended in children due to similar resistance patterns and no additive benefit [6] .

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, has been reported, with increased risk in women and obese patients. Interrupt therapy if lactic acidosis or pronounced hepatotoxicity, which may include hepatomegaly and steatosis even in the absences of marked transaminase elevations, is suspected [5]
Exacerbation of hepatitis has occurred after discontinuation of lamivudine. Most cases were self-limited, but fatalities have been reported. Monitoring for several months after treatment discontinuation is recommended [7].
Emergence of lamivudine-resistant HBV has occurred in HIV-1 infected subjects on lamivudine in the presence of concurrent infection with hepatitis B virus [8].
Pancreatitis may occur. Exercise caution in patients with a history of antiretroviral nucleoside exposure, a history of pancreatitis, of other risk factors. Discontinue treatment if signs and symptoms of pancreatitis occur [7].
Immune reconstitution syndrome has been reported with combination antiretroviral

therapy and may require further evaluation or treatment [7].
Autoimmune disorders (eg, Graves' disease, polymyositis, Guillain-Barre syndrome) have been reported in the setting of immune reconstitution. May occur many months after initiation of treatment [7]
Compared with tablets, the oral solution resulted in lower rates of virologic suppression, lower plasma lamivudine exposure, and increased development of viral resistance in pediatric patients [8].

Adverse Effects

Adverse effects reported in neonates were increased liver function tests, anemia, diarrhea, electrolyte disturbances, hypoglycemia, jaundice and hepatomegaly, rash, respiratory infections, sepsis, gastroenteritis (with associated convulsions), and transient renal insufficiency associated with dehydration. Deaths (1 from gastroenteritis with acidosis and convulsions, 1 from traumatic injury, and 1 from unknown causes) were reported in 3 neonates. [2].

Lactic acidosis: Lactic acidosis has been reported with lamivudine use. Consider discontinuing ARV drugs temporarily in patients with a lactate 2.1 to 5 mmol/L (confirmed with second test) while conducting additional diagnostic work-up. In patients with a lactate 5 mmol/L or greater (confirmed with second test) or 10 mmol/L (any one test), discontinue all ARV drugs and provide supportive therapy (eg, IV fluids, sedation, respiratory support). Following resolution of clinical and laboratory abnormalities, resume therapy with either an NRTI-sparing regimen or a revised NRTI-containing regimen. Monitor lactate monthly for 3 months or more [4].

Black Box Warning

Epivir®[5]

- Exacerbations of Hepatitis B
- Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV-1) and have discontinued lamivudine. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue lamivudine and are co-infected with HIV-1 and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted.
- Important Differences Among Lamivudine-Containing Products
- Epivir® tablets and oral solution (used to treat HIV-1 infection) contain a higher dose of the active ingredient (lamivudine) than Epivir-HBV® tablets and oral solution (used to treat chronic hepatitis B virus infection). Patients with HIV-1 infection should receive only dosage forms appropriate for treatment of HIV-1.

Monitoring

[4]

Antiretroviral Monitoring in Children (adjust schedule based on the specific antiretroviral regimen)							
	Entry into Care†	ART Initiation ††	1 to 2 weeks after initiation	2 to 4 weeks after initiation	Every 3 to 4 months †††	Every 6 to 12 months ‡	Virologic Failure (Prior to switching ARV regimen)
	If clinical, immunologic, or virologic deterioration is suspected, perform more frequent CD4 cell count and plasma viral load monitoring. If toxicity noted, perform testing more frequently until toxicity resolved						
Medical History and Physical Examination ‡‡, ‡‡‡	X	X	X	X	X		X
Adherence Evaluation ‡‡‡		X	X	X	X		X
CBC with differential †††	X	X		X	X		X
Chemistries †††, ♦♦	X	X		X	X		X
Lipid Panel ‡	X	X				X	
Random Plasma Glucose ♦♦♦		X				X	
Urinalysis	X	X				X	
CD4 count	X	X			X		X
Plasma Viral Load ♦	X	X		X	X		X
Resistance Testing	X						X
Hepatitis B screening ¶	X						X
Pregnancy Test for Girls and Young Women of Childbearing	X	X					X

Potential							
HLA-B*5701 ¶¶	X						

KEY: ARV = Antiretroviral; ART = Antiretroviral therapy; CBC = complete blood count

† If a child does not initiate ART after receiving an HIV diagnosis, the child's CD4 count and plasma viral load should be monitored at least every 3 to 4 months.

†† If ART is initiated within 30 to 90 days of a pre-therapy laboratory result, repeat testing may not be necessary.

††† CD4 cell count, CBC, and chemistries can be monitored less frequently (every 6 to 12 months) in children and youth who are adherent to therapy and have CD4 cell count values well above the threshold for opportunistic infection risk, have sustained viral suppression, and have stable clinical status for more than 2 to 3 years. Viral load testing every 3 to 4 months is generally recommended to monitor ARV adherence.

‡ If lipids have been abnormal in the past, more frequent monitoring might be needed. For patients treated with TDF, more frequent urinalysis should be considered.

‡‡ Pay special attention to changes in weight that might occur after altering an ARV regimen. Weight gain or weight loss may occur when using some ARV drugs.

‡‡‡ Virtual visits may be appropriate at some times points, particularly for adherence assessments and for visits for established patients.

♦ Some experts monitor viral load more often (with each injection) in adolescents initiating injectable cabotegravir and rilpivirine (CAB and RPV). Viral load monitoring should be performed 4 to 8 weeks after switching to long-acting CAB and RPV. HIV-RNA also should be checked in patients with unplanned missed visits and delayed dosing of long-acting CAB and RPV. When viremia develops during long-acting therapy, resistance testing, including integrase resistance testing, should be performed. Follow-up dosing in patients with missed doses should not be delayed while waiting for viral load and resistance test results. However, regimen changes should be prompted if resistance to CAB and/or RPV is discovered.

♦♦ Refers to a comprehensive metabolic panel. Some experts perform a comprehensive panel at entry and routinely test Cr, ALT, AST, with additional tests tailored to the history of the individual patient

♦♦♦ Random plasma glucose is collected in gray-top blood collection tube or other designated tube. Some experts would consider monitoring HgbA1C, rather than blood glucose, in children at risk for prediabetes/diabetes.

¶ Only recommended for individuals who have previously demonstrated no immunity to HBV and who are initiating a regimen that contains ARV drugs with activity against HBV (ie, lamivudine, emtricitabine, tenofovir alafenamide, or tenofovir disoproxil fumarate).

¶¶ Conduct HLA-B*5701 on entry prior to initiating abacavir if not done previously. Choose an alternative ARV drug if the patient is HLA-B*5701 positive.

Reference: https://clinicalinfo.hiv.gov/en/guidelines/pediatric-arv/whats-new April 2023

CD4 Cell Count and Percentages in Healthy Children							
	0 to 3 months	3 to 6 months	6 to 12 months	1 to 2 years	2 to 6 years	6 to 12 years	12 to 18 years
CD4 cell count (footnote 1)	2600 (1600 to 4000)	2850 (1800 to 4000)	2670 (1400 to 4300)	2160 (1300 to 3400)	1380 (700 to 2200)	980 (650 to 1500)	840 (530 to 1300)
CD4 percentage (footnote 1)	52 (35 to 64)	46 (35 to 56)	46 (31 to 56)	41 (32 to 51)	38 (28 to 47)	37 (31 to 47)	41 (31 to 52)
1. Values presented as median (10th to 90th percentile)							
Reference: https://clinicalinfo.hiv.gov/en/guidelines/pediatric-arv/whats-new April 2023							

Monitor for signs/symptoms of pancreatitis (eg, persistent abdominal pain, fever, nausea, vomiting, or diarrhea) [2].
Consider more frequent monitoring of viral load when treating with the solution of lamivudine [5].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

lamiVUDine (3TC) is a synthetic nucleoside analog that inhibits HIV and HBV replication by interfering with viral reverse transcriptase. It is intracellularly converted in several steps to the active compound, and then renally excreted. Poor CNS penetration with a percent CSF to serum drug concentration of approximately 12%. The oral solution is well-absorbed, with 66% bioavailability in children. Peak reached in 0.5 to 1.5 hours. Primarily eliminated as unchanged drug in the urine. The serum half-life in children is approximately 2.2 +/- 2 hours. Clearance reduced in renal impairment; dose reduction recommended. Viral resistance develops rapidly to monotherapy with lamiVUDine (3TC) [2][9].
In 36 infants up to 1 week of age administered lamiVUDine and zidovudine, lamiVUDine clearance was substantially reduced in 1-week-old neonates compared with children older than 3 months of age [2].

ABOUT

Special Considerations/Preparation

Available as an oral solution in concentrations of 5 mg/mL (Epivir-HBV®) and 10 mg/mL

(Epivir®). Oral tablets available in 100-mg (Epivir-HBV®), 150-mg (Epivir®), and 300-mg (Epivir®) strengths. **Store at room temperature.**[2][10].

Lansoprazole

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

0.73 to 1.66 mg/kg/dose orally once daily.

Uses

Crying and irritability: In otherwise healthy term infants, histamine$_2$ receptor antagonists or proton pump inhibitors should not be used for the treatment of crying and distress [1]. No improvement in crying and irritability was provided by proton pump inhibitors in infants in a systematic review of 5 randomized clinical trials (n=430) [2].

Gastroesophageal Reflux (GER): The risks associated with acid reducing agents outweighs the benefits in preterm infants for GER. Acid blocking agents should not be used and if used in preterm infants, use sparingly [3]. In otherwise healthy term infants, histamine$_2$ receptor antagonists or proton pump inhibitors should not be used for the treatment of visible regurgitation [1].
Gastroesophageal Reflux Disease (GERD): Proton pump inhibitors (PPIs) are the first-line agents for erosive esophagitis in infants and children with GERD. Histamine$_2$ receptor antagonists are the second-line agent if PPIs are not available or are contraindicated. A duration of treatment for 4 to 8 weeks for GERD symptoms is recommended. Regularly reassess the need for long-term acid suppression. If no response after 4 to 8 weeks, then re-evaluate for other causes of symptoms. H_2RAs and PPIs are not recommended for extraesophageal symptoms (e.g. cough, wheezing, asthma), unless GERD symptoms are present and/or GERD has been diagnosed [1].
A trial use of PPIs as a diagnostic test for GERD is not recommended in infants or in patients presenting with extraesophageal symptoms. However, in children with typical GERD symptoms, a trial of 4 to 8 weeks with a PPI may be used as a diagnostic test [1].

Administration

The contents of a capsule can be mixed in 40 mL of apple juice and administered by NG tube. Do not use other liquids. The NG tube should be flushed with additional apple juice after administration. Data for successfully supplying patient-specific, partial doses of lansoprazole through pediatric/neonatal feeding tubes are lacking. In one study attempting to provide a partial dose (orally disintegrating tablet formulation) through a feeding tube, a 7.5 mg dose was administered successfully through an 8 French pediatric feeding tube; however, the same dose partially clogged a 6 French pediatric feeding tube (was able to clear with NS

flush) and completely clogged a 5 French pediatric feeding tube.

There have been reports to the FDA of Teva's lansoprazole delayed-release orally disintegrating tablets causing clogged and blocked oral syringes, and gastric and jejunostomy feeding tubes requiring patients to seek emergency medical assistance to have feeding tubes unclogged or removed and replaced. Tablets may not disintegrate entirely when water is added to form a suspension, and/or the tablets may disintegrate but later form clumps which can adhere to the inside walls of the tubes. The FDA recommends that the Teva brand of delayed-release orally disintegrating lansoprazole tablets not be dispensed to patients with feeding tubes.

MEDICATION SAFETY

Contraindications/Precautions

CONTRAINDICATIONS
Contraindicated with rilpivirine-containing products [4][5].

PRECAUTIONS
Dermatologic: Severe cutaneous adverse reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and acute generalized exanthematous pustulosis, have been reported with proton pump inhibitors; discontinuation required [6]
Endocrine and metabolic: Increased serum chromogranin A (CgA) levels may occur and lead to false positive results in diagnostic investigations for neuroendocrine tumors; therapy interruption may be necessary prior to laboratory assessments [4][5].
Endocrine and metabolic: Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely with prolonged administration (in most cases, greater than 1 year) of proton pump inhibitors for at least 3 months, with most cases after a year of therapy. Concomitant use of drugs that cause hypomagnesemia may increase the risk. Monitoring is recommended during therapy. In some cases, hypomagnesemia was not reversed with magnesium supplementation and discontinuation of the proton pump inhibitor was necessary [6].
Endocrine and metabolic: Cyanocobalamin (vitamin B12) deficiency may occur with long term use [7][8].
Endocrine and metabolic: Hypomagnesemia, leading to hypocalcemia and/or hypokalemia, may occur and exacerbate underlying hypocalcemia in patients with preexisting risk of hypocalcemia (eg, hypoparathyroidism); monitoring recommended, supplementation with magnesium and/or calcium, and discontinuation may be necessary [6]
Immunologic: Increased risk of infections (necrotizing enterocolitis, pneumonia, upper respiratory tract infections, sepsis, urinary tract infections, and *Clostridium difficile* infections) in infants and children on H_2 blockers or PPIs demonstrated in case-control studies [1][9].
Immunologic: New onset or worsening cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE) have been reported with proton pump inhibitor use. Avoid using for longer than medically indicated and discontinue use if signs or symptoms of CLE or SLE develop [10][11]
Immunologic: Severe cutaneous adverse reactions, including drug reaction with eosinophilia and systemic symptoms, have been reported with proton pump inhibitors;

discontinuation required [6]
Renal: Acute tubulointerstitial nephritis has been reported and may occur at any point during therapy. May vary in presentation (symptomatic hypersensitivity reactions to non-specific symptoms of decreased renal function); discontinuation required if suspected. Diagnosis from biopsy and in the absence of extra-renal manifestations has been reported [12][13].
Respiratory: PPIs, when used for oropharyngeal dysphagia (off-label use), may be associated with an increased risk of hospitalization due to aspiration and isolated laryngeal penetration; demonstrated in a retrospective cohort (n=293 children 2 years or younger) [14].
Special populations: Use caution in patients with phenylketonuria, as oral disintegrating tablets contain phenylalanine [4][5].

Adverse Effects

Hypergastrinemia and mild transaminase elevations are the only adverse effects reported in children who received lansoprazole for extended periods of time. Available data are limited to small studies of infants and children.

In a retrospective, single-center, observational, case-control study of 136 children (1 year or older) having protracted diarrhea and stool analysis for *Clostridium difficile*, the use of PPI therapy was significantly higher in the patients with *C difficile*-associated diarrhea compared to the control group (22% vs 6%; odds ratio of 4.5 (95% CI, 1.4 to 14.4; p=0.006)) [15].

Monitoring

Observe for symptomatic improvement within 3 days. Consider intraesophageal pH monitoring to assess for efficacy (pH greater than 4.0). Measure AST and ALT if duration of therapy is greater than 8 weeks. Hypomagnesemia has been reported with prolonged administration (in most cases, greater than 1 year). Monitor magnesium levels prior to initiation of therapy and periodically during therapy in patients expected to be on long-term therapy or patients receiving concomitant drugs such as digoxin or those that may cause hypomagnesemia.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Lansoprazole inhibits gastric acid secretion by inhibition of hydrogen-potassium ATPase, the enzyme responsible for the final step in the secretion of hydrochloric acid by the gastric parietal cell ("proton pump"). Extensively metabolized in the liver by CYP 2C19 and 3A4.

Onset of action is within one hour of administration, maximal effect is at approximately 1.5 hours. Average elimination half-life is 1.5 hours. Inhibition of acid secretion is about 50% of maximum at 24 hours and the duration of action is approximately 72 hours. The absorption of weakly acidic drugs (eg, digoxin, furosemide) is enhanced. The absorption of weakly basic drugs (eg, ketoconazole) is inhibited.

ABOUT

Special Considerations/Preparation

Prevacid® is supplied as a delayed-release capsule and a delayed-release orally disintegrating tablet (ODT) containing either 15 mg or 30 mg lansoprazole for oral administration [16][17]. Lansoprazole is also supplied as a suspension through a compounding kit made by Cutis Pharma. The First ® compounding kit is available in a concentration of 3 mg/mL in the following sizes: 90 mL, 150 mL, and 300 mL. The kits contain all necessary ingredients and tools to make the suspension. The suspension is added to the lansoprazole powder in two additions; shaking well after each addition. The suspension is stable for 30 days when refrigerated (2 to 8 degrees C/ 36 to 46 degrees F) and is strawberry flavored [18].

Extemporaneous Preparation

Lansoprazole 3 mg/mL oral suspension was prepared by mixing the contents of ten 30-mg lansoprazole capsules with 100 mL of 8.4% sodium bicarbonate solution for 30 minutes. It was stored in amber-colored, plastic oral syringes. Stability was maintained for up to 7 days when refrigerated (3 to 4 degrees C) and up to 48 hours when stored at room temperature (20 to 22 degrees C). Integrity of the suspension was compromised after these storage times [19].

DOSING/ADMINISTRATION

Dose

Seizure
Loading Dose: 40 mg/kg IV loading dose; if required, a second loading dose of 20 mg/kg IV may be administered [1].

Maintenance Dose: . 40 to 60 mg/kg/day IV or orally, 3 times daily [1]

Seizure Prophylaxis; Traumatic Brain Injury (TBI)
5 days and older: 5 to 40 mg/kg/day (median, 20 mg/kg/day) IV for 7 days was used in an observational study [2]

Dosage Adjustment
Renal Impairment: There are no recommendations for neonates; however, levETIRAcetam is primarily eliminated renally [3].

Uses

Seizures: PHENobarbital is the first-line agent for treating neonatal seizures [1]. A systematic review of 5 observational studies (N=102 preterm and term neonates) demonstrated complete seizure or near-complete seizure cessation in 63% to 77% of patients with levETIRAcetam as a first- or second-line agent [7]. Seizure control was achieved in 47% of neonates treated with levETIRAcetam as a first-line agent in a retrospective chart review (n=36). Fosphenytoin or PHENobarbital was administered to 18 out of the 19 neonates who continued to have seizures. In total, 83% achieved seizure control with levETIRAcetam monotherapy or levETIRAcetam plus fosphenytoin or PHENobarbital. At least 1 dose of LORazepam was administered prior to levETIRAcetam in 28% of neonates. The mean levETIRAcetam dosages were 49.8 mg/kg IV loading dose followed by an initial maintenance dose of 24.8 mg/kg/dose IV every 12 hours. The known seizure etiologies were HIE (31%), infection (14%), and other (24%; intracranial hemorrhage, cerebral infarction, neonatal abstinence syndrome, and congenital malformations) [8].
PHENobarbital vs levETIRAcetam: The rate of achieving and maintaining electrographic seizure freedom for 24 hours in neonates was significantly higher in patients taking PHENobarbital compared with levETIRAcetam (80% vs 28%, respectively; RR 0.35, 95% CI 0.22 to 0.56) in a prospective study (N=83). The seizure-free rates at 1-hour (93% vs 49%), 48-hours (64% vs 17%), and in patients with hypoxic-ischemic encephalopathy (90% vs 35%) were also significantly lower in the PHENobarbital group. Grade 4 serious adverse effects reported included hypotension (n=5) and respiratory depression (n=1). Patients were randomized to receive loading doses of PHENobarbital 20 mg/kg or levETIRAcetam 40

mg/kg. An additional 20 mg/kg dose was given for both drugs if required 30 minutes after the start of the first dose [9].

Seizure Prophylaxis; Traumatic Brain Injury (TBI): Consider phenytoin, fosphenytoin, or levETIRAcetam as baseline (initial) care for the prevention of early posttraumatic seizures (within 7 days of injury) [10][11]. Many practitioners use levETIRAcetam for seizure prevention during the first 7 days [12], however, pediatric data are limited. Early posttraumatic seizures developed in 17.6% of 34 children, 5 days to 16 years of age, with TBI treated with 5 to 40 mg/kg/day of levETIRAcetam in a 7-day observational study [2].

Pediatric FDA Approved Indications
Tablets, Solution
• Adjunctive therapy in the treatment of partial onset seizures in children 1 month or older with epilepsy for Keppra [13]
• Monotherapy or adjunctive therapy in the treatment of partial onset seizures in children 4 years or older weighing more than 20 kg with epilepsy for Spritam [14].
• Adjunctive therapy in the treatment of myoclonic seizures in children 12 years and older with juvenile myoclonic epilepsy [15][13].
• Adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in children 6 years and older with idiopathic generalized epilepsy [15][13].

Extended-Release Tablets
• Adjunctive therapy in the treatment of partial onset seizures in children 12 years or older with epilepsy [16][17].

Intravenous (as an alternative when oral administration is not feasible)
• Monotherapy or adjunctive therapy in the treatment of partial onset seizures in children 1 month or older with epilepsy [4].
• Adjunctive therapy in the treatment of myoclonic seizures in children 12 years or older with juvenile myoclonic epilepsy [4].
• Adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in children 6 years or older with idiopathic generalized epilepsy [4].

Administration

Intravenous: Dilute in 100 mL or less of compatible diluent (do not exceed 15 mg/mL) and infuse over 15 minutes [4]. A standard concentration was 5 mg/mL or 15 mg/mL for intermittent IV administration [5].
Oral: May be given without regards to feedings [6].

MEDICATION SAFETY

Contraindications/Precautions

Precautions

Cardiovascular: Increased risk for increased diastolic blood pressure has been reported in pediatric patients 1 month to younger than 4 years [3].

Dermatologic: Serious dermatologic reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported; median onset was 14 to 17 days, but other reports were at least 4 months after initiation. Immediate discontinuation and alternative therapy recommended if these reactions occur [3]

Discontinuation: Withdraw gradually due to risk of increased seizure frequency and status epilepticus [14][19][20][4][16]; serious adverse reactions may prompt consideration for rapid discontinuation [19][20][4]

Hematologic: Hematologic abnormalities, including decreased WBC, neutrophil, and RBC counts, decreases in hemoglobin and hematocrit, and increased eosinophil count ; Agranulocytosis, pancytopenia, and thrombocytopenia have also been reported [3].

Immunologic: Anaphylaxis or angioedema may occur after the first dose or at any time during treatment; discontinuation is required [3].

Neurologic: Somnolence, fatigue, and asthenia have been reported; somnolence and asthenia typically occurred within first 4 weeks of treatment; monitoring recommended [16]

Renal: Dosage adjustments are recommended in adult patients with renal impairment [3]

Adverse Effects

Immunologic:

An anaphylactic reaction (erythematous rash, urticaria, hypotension) developed within seconds of the first dose of IV levETIRAcetam in a newborn. He was managed with epinephrine IM and cardiopulmonary resuscitation and the blood pressure returned to normal. The rash resolved approximate 24 hours later [21]

Neurologic:

After a 2 year follow-up, 280 infants who started antiepileptic agents as neonates experienced worse neurodevelopmental outcomes (cognitive and motor) with increased PHENobarbital exposure compared with levETIRAcetam in a retrospective study [22].

Psychiatric:

Behavioral disorders (typically aggression, hostility, and nervousness) were 2-fold more likely in levETIRAcetam-treated compared with placebo-treated children (1 month or older) with epilepsy in 3 randomized studies. However, behavioral deteriorations and improvements were not consistently demonstrated in 10 observational studies [23].

Solution Compatibility

NS, LR, and D_5W.

Terminal Injection Site Compatibility

Diazepam, LORazepam, and valproate sodium.

Monitoring

In one small observational study (n=38) levETIRAcetam concentrations were 12.5 to 55 mcg/mL in neonates [18]; however, there is no correlation between plasma concentration and efficacy.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action: The exact mechanism of action is unknown [3].

Concentrations
Tmax: 18.2+/-5.9 mcg/mL (1 hour after 20 mg/kg IV) and 33+/-9.8 mcg/mL (1 hours after 40 mg/kg IV) in full-term newborns [24].
Trough: 1.4 mcg/mL (before 5 mg/kg IV doses) and 2 mcg/mL (before 10 mg/kg IV doses) in full-term newborns [24].

Distribution
Protein Binding: less than 10% [3].
Vd: 0.98 L/kg (0.81 to 1.24 L/kg) in full-term newborns [24]

Metabolism: LevETIRAcetam and its major metabolite are neither inhibitors of, nor high affinity substrates for, human liver cytochrome P450 isoforms, epoxide hydrolase or UDP-glucuronidation enzymes [3].
Drug Interactions: Levetiracetam had no effect on plasma concentrations of carbamazepine, valproate, topiramate, or lamotrigine [3].

Excretion
Clearance: 0.65 mL/min/kg (day 1) and 1.33 mL/min/kg (day 7) in full-term newborns [24]. There were linear relationships between serum creatinine concentration and levETIRAcetam clearance and between creatinine clearance and levETIRAcetam clearance in a pharmacokinetic study. Clearance was 1.21 L/min/kg in 18 newborns (32 weeks gestational age or more) of median postnatal age 2 days (0 to 32 days) administered a single IV levetiracetam dose [25].

Half-Life: 15.6 hours (day 1) and 9 hours (day 7) in full-term newborns [24].
There were linear relationships between serum creatinine concentration and levETIRAcetam half-life in a pharmacokinetic study. Half-life was 8.9 hours in 18 newborns (32 weeks gestational age or more) of median postnatal age 2 days (0 to 32 days) administered a single IV levetiracetam dose [25].

ABOUT

Special Considerations/Preparation

Injection

Available: Keppra® 500 mg/5 mL (100 mg/mL) single-use vials, injection for intravenous use [4].

Preparation: Must be further diluted to a concentration not to exceed 15 mg/mL in compatible diluent prior to administration. May be stored in polyvinyl chloride (PVC) bags. The diluted solution should not be stored for more than 4 hours at controlled room temperature [4].

Oral Solution

Keppra® oral solution is available in a concentration of 100 mg/mL (dye- and alcohol-free). Store at room temperature [6] .

Extemporaneous Suspension 50 mg/mL

LevETIRAcetam suspension was stable for 91 days at 4° C and 25° C stored in amber plastic bottles prepared in Ora-Sweet and Ora-Plus [26]; for 95 days at 25° C stored in amber glass bottles, plastic bottles, or plastic syringes; and stable at 4° C in amber glass or plastic bottles when prepared in Oral Mix and Oral Mix SF.[27] :

- Triturate 500 mg levETIRAcetam tablets
- Resuspend the powder in vehicle (Oral Mix, Oral Mix SF, or 1:1 ratio of Ora-Sweet and Ora Plus)

Levothyroxine

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Hypothyroidism

Individualize the dosage and adjust based upon factors including patient age, body weight, cardiovascular status, concomitant medical conditions, coadministered food, and the specific nature of the condition being treated [1].

Peak therapeutic effect may not be attained for 4 to 6 weeks [1].

Initial oral dose: 10 to 15 mcg/kg/day orally [1]

Dosage Adjustments

At risk for cardiac failure : Consider a lower initial dose; adjust dose every 4 to 6 weeks based on patient response and TSH and total or free T4 levels [1][2][3].

Initial IV dose: 5 to 8 mcg/kg/dose every 24 hours.

Uses

Pediatric FDA Approved Indications

•Levothyroxine is indicated as a replacement or supplementation in patients with primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) congenital or acquired hypothyroidism in pediatric patients (Unithroid(R), Tirosint(R)-SOL and Synthroid(R)) [2][7][3] and in patients 6 years or older (Tirosint(R)) [8].

•As an adjunct to surgery and radioiodine therapy in the management of thyrotropin-dependent well-differentiated thyroid cancer. (Unithroid(R), Tirosint(R)-SOL and Synthroid(R)) [2][7][3] and in patients 6 years or older (Tirosint(R)) [8].

Limitations of use

•Not indicated for suppression of benign thyroid nodules and nontoxic diffuse goiter in iodine-insufficient patients or for the treatment of hypothyroidism during the recovery phase of subacute thyroiditis [2][7][3][8].

Administration

Oral[4][3]

- Single daily dose
- Administer on an empty stomach; one-half to 1 hour before breakfast
- .Should be separated by at least 4 hours from drugs that are known to impair its absorption (eg, antacids, bile acid sequestrants, calcium carbonate, cation exchange resins, ferrous sulfate, orlistat, sucralfate)

Solution:[1].

- Administer on an empty stomach, 15 minutes before breakfast.
- Administer at least 4 hours before or after drugs that are known to interfere with absorption
- Evaluate the need for dose adjustments when regularly administering within an hour of certain foods that may affect absorption
- May administer directly into mouth by squeezing content of 1 single unit-dose ampule into mouth or onto a spoon.
- May also administer in water by squeezing the contents of 1 single unit-dose ampule into a cup of water; stir and drink immediately. Rinse cup with more water and drink.
- Do not dilute in other liquids or food
- Open the ampule and prepare the solution immediately before intake

Tablets: May crush and suspend in 5 to 10 mL of water prior to administration (eg, for infants and children who cannot swallow intact table); do not store suspension. Do not suspend in other liquids or food (eg, soybean-based infant formula) [3]

Injection
Intravenous powder for solution: Final concentrations are approximately 20 mcg/mL or 100 mcg/mL. **Do not add to any other IV solution** [5].
Intravenous solution: Do not exceed an IV administration rate of 100 mcg/min. **Do not add to any other IV solution** [6]

MEDICATION SAFETY

Contraindications/Precautions

CONTRAINDICATIONS
•Hypersensitivity to thyroid hormone or any component of the product [10]
•Hypersensitivity to glycerol (oral solution) [1]
•Uncorrected adrenal insufficiency; may precipitate acute adrenal crisis [1][2][3][11]

PRECAUTIONS
Cardiovascular: New or worsening cardiac abnormalities, such as increase in heart rate, angina and arrhythmias may develop with overtreatment; reduce or stop therapy for one week and then cautiously restart at lower dose [1][9][2][11][10]
Cardiovascular: Underlying cardiovascular disease; initiate therapy at lower dose [1][9] [2][11][10]; monitoring recommended [6]

Cardiovascular: Surgical procedures in patients with preexisting coronary artery disease increases risk of cardiac arrhythmias; monitoring recommended [10][9][2][11]
Endocrine and metabolic: Use of doses above recommended range, including excessive bolus doses greater than 500 mcg, increase risk of serious or life-threatening manifestations of toxicity; monitoring recommended and consider dose adjustment [6]
Endocrine and metabolic: Chronic autoimmune thyroiditis, with progression to myxedema or acute adrenal crisis, may occur in association with other autoimmune disorders, such as adrenal insufficiency, diabetes mellitus, and pernicious anemia; treat with replacement glucocorticoids prior to initiation of levothyroxine and monitoring is recommended [6]
Endocrine and metabolic: Myxedema coma may result in unpredictable absorption of levothyroxine sodium from the gastrointestinal tract. Administer thyroid hormone products formulated for IV administration to treat myxedema coma [1].[9][2]
Endocrine and metabolic: Concomitant adrenal insufficiency; treat with replacement glucocorticoids prior to initiation of levothyroxine to avoid acute adrenal crisis [1][9] [6][11][10]
Endocrine and metabolic: Worsening glycemic control in diabetic patients may occur; monitoring recommended [1][9][2]
Musculoskeletal: Overtreatment may cause craniosynostosis and acceleration of bone age in pediatric patients with congenital or acquired hypothyroidism [1][9].
Musculoskeletal: Increased bone resorption and decreased bone mineral density may occur with greater than replacement doses [1][7].
Special populations: Undertreatment may cause adverse effects on cognitive development and linear growth in pediatric patients with congenital or acquired hypothyroidism [1][9].

Adverse Effects

Prolonged over-treatment can produce premature craniosynostosis and acceleration of bone age.

Black Box Warning

Thyroid hormones, including levothyroxine, either alone or with other therapeutic agents should not be used for the treatment of obesity or for weight loss.
In euthyroid patients, doses within the range of daily hormonal requirements are ineffective for weight loss.
Larger doses may produce serious or life-threatening manifestations of toxicity, especially when given in combination with sympathomimetic amines such as those used for their anorectic effects [9].

Monitoring

After 2 weeks of treatment, serum levothyroxine (T_4) concentration should be in the high normal range (10 to 16 mcg/dL) and should be maintained in this range for the first year of

life. Serum triiodothyronine (T_3) concentration should be normal (70 to 220 nanograms/dL), and TSH should have declined from initial value. After 12 weeks of treatment, serum TSH concentration should be in the normal range, less than 15 milliunits/L. Serum T_4 and TSH concentrations should be measured at two weeks of age, then every 1 to 2 months, or 2 weeks after any change in dosage. Assess for signs of hypothyroidism: Lethargy, poor feeding, constipation, intermittent cyanosis, and prolonged neonatal jaundice. Assess for signs of thyrotoxicosis: hyperreactivity, altered sleep pattern, tachycardia, tachypnea, fever, exophthalmos, and goiter. Periodically assess growth, development, and bone-age advancement.
Closely monitor infants during the first two weeks of therapy for cardiac overload and arrhythmias [1].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action: Tissue deiodination converts T_4 to T_3, the active metabolite.

Bioavailability of oral levothyroxine is approximately 40% to 80%. Absorption increased in fasting state. Circulating thyroid hormones are 99% bound to plasma proteins. Only unbound hormone is metabolically active. Major pathway of metabolism is through deiodination. Also metabolized via conjugation with glucuronides and sulfates playing a role. Primarily eliminated in the urine with approximately 20% eliminated in the stool. Half-life is 6 to 7 days for oral levothyroxine (T_4), and 2 days or less for liothyronine (T_3); peak therapeutic effect may not be reached until 4 to 6 weeks due to its long half-life. Levothyroxine IV produces effects in 6 to 8 hours, with full therapeutic effect within 24 hours. Levothyroxine IV also produces a predictable hormone level in the reservoir with a 7 day half-life, thus no need for multiple injections; daily injections of lesser amounts of levothyroxine are sufficient until daily oral dose accepted by the patient [4] .

ABOUT

Special Considerations/Preparation

Oral
Availability: levothyroxine sodium 13 to 200 mcg/mL clear oral solution [1], scored tablets ranging from 25 to 300 mcg per tablet [3]. Also available in capsules that contain a viscous liquid ranging from 13 to 150 mcg per capsule. **Capsules cannot be crushed, suspended in water, or dissolved by placing in water before use**. Monitor patient closely when switching brand of drug due to some differences in bioavailability.

Extemporaneous Oral Suspension
•To prepare a **15-mcg/mL levothyroxine oral suspension**: Crush levothyroxine 100-mcg

tablets in glycerol and add sterile water up to desired volume. Shake well before dispensing. Product stability is 10 days when refrigerated between 2 and 8 degrees C. Stability tests demonstrated a 12% decline in levothyroxine concentration in the prepared suspension over 11 days.

To prepare a **25 mcg/mL levothyroxine sodium suspension**[12]:

- Crush and grind 200 mcg levothyroxine tablets to a fine powder in a mortar with a pestle.
- Mix powder in a suitable vehicle suspension (1:10 Simple syrup NF and 1% methylcellulose or 1:1 OraSweet and OraPlus).
- When refrigerated at 4 degrees C in amber polyethylenephthalate bottles, the suspension was stable for two weeks (14 days) and at 25 degrees C for up to one week (7 days)

•An oral liquid formulation of **levothyroxine sodium 25 mcg/mL** in 40% glycerol compounded from crushed tablets and distilled water with no preservatives added was stable for 8 days when stored in amber bottles at 4 degrees C. Degradation occurred faster in the formulation with preservative (methylparaben).

Injection

Powder for solution: Lyophilized powder in vials containing 100 or 500 mcg. **Use only NS for reconstitution.** Following reconstitution with 5 mL of NS, final concentrations are approximately 20 mcg/mL and 100 mcg/mL **Use immediately. Do not add to any other IV solution.** Reconstituted solution is preservative free and stable for 4 hours [5].
Solution: Levothyroxine is available as a solution in single-dose vials containing 20, 40, or 100 mcg/mL [6]

Lidocaine - Antiarrhythmic

DOSING/ADMINISTRATION

Dose

Initial bolus dose: 0.5 to 1 mg/kg IV push over 5 minutes. Repeat every 10 minutes as necessary to control arrhythmia. **Maximum total bolus dose should not exceed 5 mg/kg.**

Maintenance IV infusion: 10 to 50 mcg/kg/minute. Premature neonates should receive lowest dosage.

Uses

Short-term control of ventricular arrhythmias, including ventricular tachycardia, premature ventricular contractions, and arrhythmias resulting from digitalis intoxication.

Administration

The concentration for an IV push dose is 1 to 20 mg/mL. For continuous infusion, dilute in compatible solution to concentration of 0.8 to 8 mg/mL or use available premixed solutions (4 to 8 mg/mL) [1][2].

Solution Preparation Calculations
To calculate the AMOUNT of drug needed per defined final fluid volume:
Desired final concentration (mg/mL) x defined final fluid volume (mL) = AMOUNT of drug to add to final infusion solution (mg).
To calculate the VOLUME of drug needed per defined final fluid volume:
*AMOUNT of drug to add (mg) ÷ drug (vial) concentration (mg/mL) = VOLUME of drug to add (mL)
Example (for Lidocaine): Mix 50 mL of 2400 mcg/mL solution using lidocaine concentration of 20 mg/mL.
2400 mcg/mL = 2.4 mg/mL
2.4 mg/mL x 50 mL = 120 mg lidocaine
***120 mg ÷ 20 mg/mL = 6 mL of lidocaine**
Add 6 mL of lidocaine (20 mg/mL) to 44 mL of compatible solution (eg, D_5W) to yield 50 mL of infusion solution with a concentration of 2400 mcg/mL.

Lidocaine Titration Chart		
Concentration (mcg/mL)	**Dose (mcg/kg/min)**	**IV Rate (mL/kg/hour)**
800	10	0.75
	20	1.5
	30	2.25
	40	3
	50	3.75
1600	10	0.375
	20	0.75
	30	1.125
	40	1.5
	50	1.875
2400	10	0.25
	20	0.5
	30	0.75
	40	1
	50	1.25
4000	10	0.15
	20	0.3
	30	0.45
	40	0.6
	50	0.75
6000	10	0.1
	20	0.2
	30	0.3
	40	0.4
	50	0.5
8000	10	0.075
	20	0.15
	30	0.225
	40	0.3
	50	0.375

MEDICATION SAFETY

Contraindications/Precautions

CONTRAINDICATIONS

- Stokes-Adams syndrome[4].
- Wolff-Parkinson-White Syndrome [4].
- Severe degrees of sinoatrial, atrioventricular, or intraventricular block [4].
- Known hypersensitivity to local anesthetics of the amide type [4]

PRECAUTIONS

Cardiovascular: Acceleration of ventricular rate may occur, particularly in patients with atrial fibrillation or flutter [4]

Cardiovascular: More frequent or serious ventricular arrhythmias or complete heart block may occur in patients with sinus bradycardia, or incomplete heart block without prior acceleration in heart rate [4]
Endocrine and metabolic: Malignant hyperthermia may occur; discontinue use immediately and institute countermeasures [4]
Hematologic: Methemoglobinemia has been reported with local anesthetic use; increased risk in patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites; close monitoring recommended in these patients [5]
Hepatic: Possible increased risk of toxicity in patients with impaired hepatic function [4]
Immunologic: Hypersensitivity reactions have been reported; immediate discontinuation required [4]
Musculoskeletal: Chondrolysis may occur with intraarticular infusions following arthroscopic or other surgical procedures (unapproved use) [6]
Renal: Possible increased risk of toxicity in patients with impaired renal function [4]
Special Populations: Viscous lidocaine is not recommended or approved for teething pain [7][8]. Seizures, cardiopulmonary arrest, and death have been associated with the use of viscous lidocaine for teething pain or oral irritation in infants and children [9][10][11].

Adverse Effects

Early signs of CNS toxicity are drowsiness, agitation, vomiting, and muscle twitching. Later signs include seizures, loss of consciousness, respiratory depression, and apnea. Cardiac toxicity is associated with excessive doses and includes bradycardia, hypotension, heart block, and cardiovascular collapse.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Alteplase, aminophylline, amiodarone, ampicillin, caffeine citrate, calcium chloride, calcium gluconate, cefazolin, cefoxitin, chloramphenicol, cimetidine, dexamethasone, digoxin, dobutamine, dopamine, enalaprilat, erythromycin lactobionate, famotidine, fentanyl, flumazenil, furosemide, glycopyrrolate, heparin, hydrocortisone succinate, insulin, linezolid, methicillin, metoclopramide, micafungin, morphine, nafcillin, nicardipine, nitroglycerin, penicillin G, pentobarbital, potassium chloride, procainamide, ranitidine, sodium bicarbonate, and sodium nitroprusside.

Terminal Injection Site Incompatibility

Phenytoin.

Monitoring

Continuous monitoring of ECG, heart rate, and blood pressure should be performed. Assess level of consciousness. Observe for seizure activity. Therapeutic drug concentration is 1.5 to 6 mg/L, with toxicity associated with concentrations greater than 9 mg/L [3][2].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Lidocaine is a type 1b antiarrhythmic agent used intravenously. Onset of action is 1 to 2 minutes after bolus administration. Plasma half-life in neonates is 3 hours. Free drug fraction in both term and premature neonates is approximately twice that found in older children because of significantly reduced protein binding by α_1-acid glycoprotein. Transformed in the liver to metabolites with antiarrhythmic activity; approximately 30% is excreted unchanged in neonates.

ABOUT

Special Considerations/Preparation

Use only preservative-free lidocaine without EPINEPHrine.
Availability: Multiple concentrations ranging from 1% to 20%. Concentrations of 10% (100 mg/mL) and 20% (200 mg/mL) must be diluted [4][6]. Premixed solutions for continuous infusion, 4 mg/mL (0.4%) and 8 mg/mL (0.8%) [4].
Storage: Store at a room temperature of 20 to 25 degrees C [4]. Avoid excessive heat [4] and protect from light [6]
Dilution: To make a dilution for bolus dosing, dilute 10 mg lidocaine (0.5 mL of 2% solution) in 9.5 mL NS or D_5W, yielding a 1-mg/mL final concentration.

Lidocaine - CNS

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Term, normothermic newborns:
Loading dose: 2 mg/kg IV, followed immediately by maintenance infusion.
Maintenance infusion: 6 mg/kg per hour for 6 hours, then 4 mg/kg per hour for 12 hours, then 2 mg/kg per hour for 12 hours.

Caution: Preterm newborns and term newborns undergoing hypothermia treatment are at risk for drug accumulation due to slower drug clearance. Precise dosing in these infants is uncertain.

Uses

Treatment of severe recurrent or prolonged seizures that do not respond to first-line therapies.

Administration

Administer loading dose as an IV bolus over 10 minutes at a concentration not exceeding 20 mg/mL. For continuous infusion, dilute in compatible diluent to a concentration of 0.8 to **not exceeding 8 mg/mL** or use available premixed solutions (4 to 8 mg/mL) [1][2][3].

MEDICATION SAFETY

Contraindications/Precautions

CONTRAINDICATIONS
•Stokes-Adams syndrome[4].
•Wolff-Parkinson-White Syndrome [4].
•Severe degrees of sinoatrial, atrioventricular, or intraventricular block [4].
•Known hypersensitivity to local anesthetics of the amide type [4]

PRECAUTIONS
Cardiovascular: Acceleration of ventricular rate may occur, particularly in patients with

atrial fibrillation or flutter [4]
Cardiovascular: More frequent or serious ventricular arrhythmias or complete heart block may occur in patients with sinus bradycardia, or incomplete heart block without prior acceleration in heart rate [4]
Endocrine and metabolic: Malignant hyperthermia may occur; discontinue use immediately and institute countermeasures [4]
Hematologic: Methemoglobinemia has been reported with local anesthetic use; increased risk in patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites; close monitoring recommended in these patients [5]
Hepatic: Possible increased risk of toxicity in patients with impaired hepatic function [4]
Immunologic: Hypersensitivity reactions have been reported; immediate discontinuation required [4]
Musculoskeletal: Chondrolysis may occur with intraarticular infusions following arthroscopic or other surgical procedures (unapproved use) [6]
Renal: Possible increased risk of toxicity in patients with impaired renal function [4]
Special Populations: Viscous lidocaine is not recommended or approved for teething pain [7][8]. Seizures, cardiopulmonary arrest, and death have been associated with the use of viscous lidocaine for teething pain or oral irritation in infants and children [9][10][11].

Adverse Effects

Do not use concurrently with phenytoin due to cardiac effects. Stop infusion immediately if significant cardiac arrhythmia occurs. Arrhythmias and significant bradycardia have occurred in 5% of reported cases. Slowing of the heart rate is common.

In a retrospective study (n=521), the incidence of cardiac events with lidocaine treatment for seizures in term and preterm infants was 1.3% to 1.9%. Cardiac events included bradycardia (n=6) with 2:1 AV block in 2 infants and QRS prolongation in 1 infant. Irregular heart rate occurred in 2 infants, decreased heart rate not fulfilling bradycardia criteria occurred in 3, with a prolonged QT interval in 1 infant, and ventricular extrasystoles were reported in 2 infants. Tachycardia, hypotension, and asystole following bradycardia were reported in 1 infant each [12].

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Alteplase, aminophylline, amiodarone, ampicillin, caffeine citrate, calcium chloride, calcium

gluconate, cefazolin, cefoxitin, chloramphenicol, cimetidine, dexamethasone, digoxin, dobutamine, dopamine, enalaprilat, erythromycin lactobionate, famotidine, fentanyl, flumazenil, furosemide, glycopyrrolate, heparin, hydrocortisone succinate, insulin, linezolid, metoclopramide, micafungin, morphine, nafcillin, nicardipine, nitroglycerin, penicillin G, pentobarbital, potassium chloride, procainamide, ranitidine, sodium bicarbonate, and sodium nitroprusside.

Terminal Injection Site Incompatibility

Phenytoin.

Monitoring

Continuous monitoring of EKG, heart rate, and blood pressure. Observe for worsening of seizure activity. Measuring blood concentrations is not clinically useful except when accumulation is suspected.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

The mode of action for lidocaine as an anticonvulsant drug is unknown. Lidocaine is metabolized in the liver into 2 active metabolites: monoethylglycinexylidide (MEGX) and glycinxylidide (GX). Approximately 30% is excreted unchanged in the urine. The half-life in neonates is at least 3 hours, and clearance is dose-dependent. The clinically effective dose of 6 mg/kg/hr will lead to accumulation of both lidocaine and metabolites within several hours. Free drug fraction in both term and premature neonates is approximately twice that found in older children because of significantly reduced protein binding by alpha 1-acid glycoprotein.

ABOUT

Special Considerations/Preparation

Use only preservative-free lidocaine without EPINEPHrine.
Availability: Multiple concentrations ranging from 1% to 20%. Concentrations of 10% (100 mg/mL) and 20% (200 mg/mL) must be diluted [4][6]. Premixed solutions for continuous infusion, 4 mg/mL (0.4%) and 8 mg/mL (0.8%) [4].
Storage: Store at a room temperature of 20 to 25 degrees C [4]. Avoid excessive heat [4]

and protect from light [6]
Dilution: To make a dilution for bolus dosing, dilute 10 mg lidocaine (0.5 mL of 2% solution) in 9.5 mL NS or D_5W, yielding a 1-mg/mL final concentration.

Lidocaine/Prilocaine

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Do not use in infant younger than 12 months who is receiving treatment with methemoglobin-inducing agents which include drugs in classes of nitrates/nitrites, local anesthetics, antineoplastic agents, antibiotics, antimalarials, anticonvulsants, and other drugs[1]
37 weeks' gestation or older:Maximum total dose of 1 g applied to maximum application area of 10 cm^2 for maximum application time of 1 hour [1]

Uses

Pediatric FDA Approved Indications
Topical anesthetic for use on normal intact skin for local analgesia and genital mucous membranes for superficial minor surgery and as pretreatment for infiltration anesthesia [1].
Not recommended for any clinical situation where penetration or migration beyond the tympanic membrane into the middle ear is possible due to risk of ototoxic effects [1]
Evaluated in 105 full-term neonates for blood drawing and circumcision procedures. Studies have not demonstrated efficacy for heel lancing [1].

MEDICATION SAFETY

Contraindications/Precautions

CONTRAINDICATIONS
Hypersensitivity to local amide-type anesthetics or to any component of the product [1]

PRECAUTIONS
Concomitant Use: with class III anti-arrhythmic drugs (e.g. amiodarone, bretylium, sotalol, dofetilide) may result in additive cardiac effects; monitoring recommended [1].
Dermatologic: Increased risk for systemic absorption and toxicity with covering of application site, large doses and/or treatment areas, skin temperature increases, and with irritated, broken skin, or wounds; potentially resulting in life-threatening side effects [2][3]
Hematologic: Methemoglobinemia has been reported with use of local anesthetics; increased risk in patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites and other drugs

associated with methemoglobinemia; if use is required in at-risk patients monitoring is recommended; medical management and discontinuation of therapy is required [1].
Hepatic: Risk of toxic plasma concentrations in patients with severe hepatic disease [1]
Immunologic: Use with caution in patients with history of allergies to paraaminobenzoic acid derivatives (procaine, tetracaine, benzocaine, etc.) [1]
Immunologic: Has been shown to inhibit viral and bacterial growth, effect on intradermal injections of live vaccines has not been determined [1]
Ophthalmic: Avoid contact with eyes due to risk of severe irritation and loss of protective reflexes [1]
Otic: Ototoxic effects possible when drug penetrates beyond the tympanic membrane into the middle ear [1]
Special populations: Acutely ill or debilitated patients; increased sensitivity to systemic effects [1]

Adverse Effects

Blanching and redness resolve without treatment. When measured, blood levels of methemoglobin in neonates after the application of 1 g of EMLA cream have been well below toxic levels. Two cases of methemoglobinemia in infants occurred after greater than 3 g of EMLA cream was applied; in 1 of these cases, the infant also was receiving sulfamethoxazole. EMLA cream should not be used in neonates with congenital or idiopathic methemoglobinemia, or who are receiving other drugs known to induce methemoglobinemia: sulfonamides, acetaminophen, nitrates, nitroglycerin, nitroprusside, phenobarbital, and phenytoin.

Monitoring

Blood methemoglobin concentration if concerned about toxicity.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

EMLA cream, containing 2.5% lidocaine and 2.5% prilocaine, attenuates the pain response to circumcision when applied 60 to 90 minutes before the procedure. The analgesic effect is limited during the phases associated with extensive tissue trauma such as during lysis of adhesions and tightening of the clamp. Stabilizes the neuronal membranes by inhibiting the ionic fluxes required for conduction and initiation of nerve impulses. There is a theoretic concern about the potential for neonates to develop methemoglobinemia after the application of EMLA cream, because a metabolite of prilocaine can oxidize hemoglobin to methemoglobin. Neonates are deficient in methemoglobin NADH cytochrome b_5 reductase.

Lidocaine is metabolized rapidly by the liver to a number of active metabolites and then excreted renally.

ABOUT

Special Considerations/Preparation

Available in 5-g and 30-g tubes with Tegaderm dressing. Each gram of EMLA contains lidocaine 25 mg and prilocaine 25 mg in a eutectic mixture. pH of the product is 9. Contains no preservatives.

Linezolid

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Usual dose, 10 mg/kg/dose IV or orally every 8 hours [1][2].
Preterm newborns less than 1 week of age: 10 mg/kg/dose IV or orally every 12 hours [1].

Anthrax[3]
32 up to 34 weeks gestational age
0 to 1 week: 10 mg/kg/dose IV or oral every 12 hours.
1 to 4 weeks: 10 mg/kg/dose IV or oral every 8 hours.
34 weeks or more gestational age
0 to 4 weeks: 10 mg/kg/dose IV or oral every 8 hours
Duration: 2 to 3 weeks or more until stable as IV triple therapy for systemic anthrax (anthrax meningitis or disseminated infection and meningitis cannot be ruled out) or as IV combination therapy for systemic anthrax when meningitis is ruled out. Continue antimicrobial course of prophylaxis (usually oral therapy) for up to 60 days from onset of illness [3].

Dose Adjustments
Renal impairment: No adjustment is necessary; however, the 2 primary metabolites of linezolid may accumulate in patients with renal insufficiency [4].
Hepatic impairment
Mild to moderate (Child-Pugh A or B): No adjustment is necessary. Pharmacokinetics in patients with severe hepatic failure have not been evaluated [4].
Dialysis: Administer after hemodialysis [4]

Uses

Limited to treatment of infections, including endocarditis and ventriculitis, caused by gram positive organisms (eg, methicillin-resistant *Staph. aureus,*, penicillin-resistant *Strep. pneumoniae*, and vancomycin-resistant *Enterococcus faecium)* that are refractory to conventional therapy with vancomycin and other antibiotics [5][6][7][2]. Do not use as empiric treatment or in any patient with infections caused by gram-negative organisms.

Anthrax: Intravenous linezolid is recommended for neonates 32 week gestational age or older for the following [3]:

Systemic Anthrax when meningitis can be ruled out (IV)
Combination IV Therapy
- **Preferred:** Ciprofloxacin. *Alternatives in order of preference: meropenem, levofloxacin,*

imipenem/cilastatin, or vancomycin. If strains are penicillin-susceptible, then penicillin G (preferred) or ampicillin (alternative).

- **Plus**
- **Preferred:** Clindamycin *Alternatives in order of preference: linezolid, doxycycline (not for neonates 37 weeks gestation or younger), or rifampin.*

Systemic Anthrax (meningitis or disseminated infection and meningitis cannot be ruled out) (IV)
Triple IV Therapy

- **Preferred:** Ciprofloxacin. *Alternatives in order of preference: levofloxacin or moxifloxacin*
- **Plus**
- **Preferred:** Meropenem. *Alternatives in order of preference: imipenem/cilastatin or doripenem. If strains are penicillin-susceptible, then penicillin G (preferred) or ampicillin (alternative).*
- **Plus**
- **Preferred:** Linezolid. *Alternatives in order of preference: clindamycin or rifampin or as a last resort, chloramphenicol*

Oral follow-up therapy for severe anthrax
Combination Oral Therapy

- **Preferred:** Ciprofloxacin. *Alternative: levofloxacin. If strains are penicillin- susceptible, amoxicillin (preferred) or penicillin VK (alternative).*
- **Plus**
- **Preferred:** Clindamycin. *Alternatives in order of preference: doxycycline (not for neonates 37 weeks gestation or younger) or linezolid.*

Administration

IV: Give as an intermittent IV infusion over 30 to 120 minutes. Supplied as ready-to-use infusion bags (2 mg/mL); no further dilution is necessary [1].
Oral: May administer without regard to timing of feedings. Before administering oral suspension, gently mix by inverting bottle 3 to 5 times. Do not shake [1].

MEDICATION SAFETY

Contraindications/Precautions

Contraindications
Concomitant use of MAOIs or use within 2 weeks of taking an MAOI such as phenelzine or

isocarboxazid [10]

Precautions
Carcinoid syndrome: Use not recommended unless clinically necessary [11]
Cardiovascular: Uncontrolled hypertension; use not recommended unless patients monitored for potential blood pressure increases [11]
Concomitant use: Concomitant use of indirectly or directly acting sympathomimetic agents such as pseudoephedrine, vasopressive agents such as epinephrine and norepinephrine, or dopaminergic agents such as dopamine and dobutamine is not recommended unless patients are monitored for potential blood pressure increases [11]
Concomitant use: Concomitant use of SSRIs, tricyclic antidepressants, serotonin 5-HT1 receptor agonists (triptans), bupropion, buspirone, or opioids (including meperidine) not recommended unless clinically necessary; monitoring required if coadministration necessary [12]
Endocrine and metabolic: Lactic acidosis has been reported; immediately evaluate patients who develop recurrent nausea or vomiting, unexplained acidosis, or a low bicarbonate level [1]
Endocrine and metabolic: Lactic acidosis has been reported in a case series of 3 children aged 6 months, 6 months, and 16 years receiving linezolid for 53, 31 and 7 days of treatment, respectively. All 3 children had liver dysfunction and complicated medical courses while receiving linezolid therapy. Two patients developed multiple system organ failure and metabolic acidosis, and the third patient developed pressor-refractory shock and metabolic acidosis. The role of linezolid in the development of lactic acidosis in these patients is unknown [8].
Endocrine and metabolic: Symptomatic hypoglycemia has been reported in diabetic patients receiving concomitant insulin or oral hypoglycemic agents; dose adjustment or discontinuation may be required [1]
Endocrine and metabolic: Thyrotoxicosis; use not recommended unless patients monitored for potential blood pressure increases [11]
Endocrine and metabolic: Pheochromocytoma; use not recommended unless patients monitored for potential blood pressure increases [11]
Endocrine and metabolic: Hyponatremia and SIADH has been reported; monitoring recommended and discontinuation and supportive therapy may be necessary [13]
Gastrointestinal: Clostridioides difficile-associated diarrhea (CDAD) has been reported and may range from mild diarrhea to fatal colitis; consider CDAD in all patients presenting with diarrhea following antibacterial use. Careful evaluation, monitoring, and treatment or surgical intervention may be necessary; discontinuation may be needed [10].
Hematologic: Myelosuppression in the form of anemia, leukopenia, pancytopenia, and thrombocytopenia has been reported especially during treatment longer than 2 weeks; monitoring recommended [14]
Hematologic: Myelosuppression may occur in patients with chronic infection during concomitant or prior antibacterial therapy or with concomitant use of bone marrow-suppressing drugs; monitoring recommended [14]
Immunologic: Catheter-related bloodstream infections or catheter-site infections; use not recommended [1]
Neurologic: Convulsions may occur in patients with history or risk factors for seizure [1]
Neurologic: Peripheral and optic neuropathy may occur especially in patients treated longer than 28 days [1]
Ophthalmic: Visual disturbances such as changes in visual acuity or color vision, blurred vision, and visual field defects have been reported; monitoring recommended [1]

Pediatric: Patients with CNS infections; use not recommended [1]
Phenylketonuria: Oral suspension contains 20 mg phenylalanine per 5 mL which may be harmful to patients with phenylketonuria; consider the combined about of phenylalanine from all sources prior to prescribing oral suspension [10].
Serotonin syndrome: Fatal cases has been reported with concomitant use of serotonergic agents; monitoring and immediate discontinuation of serotonergic agent required [11]

The FDA issued an alert regarding Zyvox (linezolid) on March 16, 2007. Patients in an open-label, randomized trial comparing linezolid with vancomycin, oxacillin, or dicloxacillin in the treatment of seriously ill patients with intravascular catheter-related bloodstream infections had a higher chance of death than did patients treated with any comparator antibiotic, and the chance of death was related to the type of organism causing the infection. Patients with Gram positive infections had no difference in mortality according to their antibiotic treatment. In contrast, mortality was higher in patients treated with linezolid who were infected with Gram negative organisms alone, with both Gram positive and Gram negative organisms, or who had no infection when they entered the study. See http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm101503.htm.

Adverse Effects

Elevated transaminases and diarrhea occur in approximately 5% of treated patients; thrombocytopenia and anemia occur in 2% to 5% [2][15].
Sideroblastic anemia and severe cutaneous adverse reactions such as toxic epidermal necrolysis and Stevens-Johnson syndrome have been reported during postmarketing surveillance [16].

Solution Compatibility

D_5W, NS, Lactated Ringers.

Terminal Injection Site Compatibility

Acyclovir, amikacin, aminophylline, ampicillin, aztreonam, calcium gluconate, caspofungin, cefazolin, cefoxitin, ceftazidime, ceftriaxone, cefuroxime, cimetidine, clindamycin, dexamethasone, digoxin, dobutamine, dopamine, enalaprilat, esmolol, famotidine, fentanyl, fluconazole, furosemide, ganciclovir, gentamicin, heparin, hydrocortisone succinate, imipenem/cilastatin, lidocaine, lorazepam, magnesium sulfate, meropenem, methylprednisolone, metoclopramide, metronidazole, mezlocillin, midazolam, morphine, naloxone, netilmicin, nicardipine, nitroglycerin, pentobarbital, phenobarbital, piperacillin, piperacillin-tazobactam, potassium chloride, propranolol, ranitidine, remifentanil, sodium bicarbonate, theophylline, ticarcillin, tobramycin, vancomycin, vecuronium, and zidovudine.

Terminal Injection Site Incompatibility

Amphotericin B, erythromycin lactobionate, phenytoin, and trimethoprim/sulfamethoxazole.

Monitoring

Monitor CBC weekly, especially in patients receiving linezolid for longer than 2 weeks, those with myelosuppression, those receiving concurrent myelosuppressive drugs, or those with a chronic infection who have received previous or concomitant antibiotic therapy [1]. Monitor lactate concentrations in patients receiving extended courses of linezolid therapy or in patients with pre-existing hepatic or renal dysfunction [8]. Patients receiving an extended course of therapy (eg, over 28 days) should be monitored for signs and symptoms of neuropathy [9]. Monitor for signs and symptoms of serotonin syndrome (hyperpyrexia, hyperreflexia, and incoordination) in patients receiving concomitant serotonergic agents. Visual function should be assessed in patients receiving long-term linezolid (3 months or greater) and in all patients experiencing visual impairment. Monitor blood pressure in patients with uncontrolled hypertension, pheochromocytoma, thyrotoxicosis, and/or in patients receiving sympathomimetic agents, vasopressive agents, or dopaminergic agents [1].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Linezolid is an oxazolidinone agent that has a unique mechanism of inhibition of bacterial protein synthesis. It is usually bacteriostatic, although it may be bactericidal against *S. pneumoniae*, *B. fragilis*, and *C. perfringens*. Resistance to linezolid has been reported for vancomycin-resistant *E. faecium* and methicillin-resistant *S. aureus*[17][18][19][20][21]. Outbreaks of linezolid-resistant *S. aureus*, *S. epidermidis*, and *S. haemolyticus* have been reported in adult ICU settings. The majority of patients had received linezolid previously [22][23][17].

Rapidly penetrates osteoarticular tissues and synovial fluid. CSF concentrations were 70% of plasma concentrations in older patients with non-inflamed meninges. Completely and rapidly absorbed when administered orally to adults and children. Metabolized by oxidation without cytochrome CYP induction. Excreted in the urine as unchanged drug (30%) and two inactive metabolites. Serum half-life in most neonates is 2 to 3 hours, with the exception of preterm neonates less than one week of age, who have a serum half-life of 5 to 6 hours [1][24][25].

Neonate study: Linezolid plasma concentrations were greater or equal to the MIC (1 to 2

mg/L) in 15 of 16 extremely premature (mean gestational age, 28 weeks) neonates (mean postnatal age at beginning of treatment, 3 weeks) administered either oral or IV linezolid. The dosages of linezolid were 10 mg/kg orally every 8 hours or 30 mg/kg/day by continuous IV. Trough concentrations were measured for the oral route [26].

ABOUT

Special Considerations/Preparation

Intravenous
Availability: 2 mg/mL solution in single-dose, ready-to-use 100 mL and 300 mL flexible plastic infusion bags in a foil laminate overwrap [10]
Storage: Store infusion bags at a room temperature of 25 degrees C (77 degrees). Protect from light and freezing. Keep bags in the overwrap until ready to use. Discard unused portion [10]

Oral
Powder for Suspension
Availability: After reconstitution each bottle will contain 150 mL of orange-flavored suspension providing 100 mg/5 mL [10]
Storage: Store powder for suspension in tightly closed bottle at a room temperature of 25 degrees C (77 degrees F). Protect from light and moisture. Store reconstituted suspension at room temperature. Use within 21 days after reconstitution .[10].
Tablets
Availability: 600 mg film-coated tablet [10]
Storage: Store in tightly closed bottle at a room temperature of 25 degrees C (77 degrees F). Protect from light and moisture [10].

Preparation of Suspension
To reconstitute the oral suspension, add 123 mL distilled water (final concentration, 100 mg/5 mL) in 2 portions, shaking between each portion. After reconstitution, invert the bottle gently 3 to 5 times before each use but **do NOT shake**. Reconstituted solution should be used within 21 days when stored at room temperature [10].

Lopinavir/Ritonavir

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

HIV Infection
14 days or older: Lopinavir 16 mg/kg and ritonavir 4 mg/kg orally twice daily OR lopinavir 300 mg/m^2 and ritonavir 75 mg/m^2 orally twice daily [1][2][3].
Do not use until a postmenstrual age of 42 weeks [2].

Once-daily lopinavir/ritonavir is NOT recommended in any pediatric patient [2].

Co-administration with efavirenz, nevirapine, or nelfinavir is NOT recommended in patients younger than 6 months of age [4].

When used in infants and young children, especially those 14 days to 6 months of age, it is critical to ensure that dose calculation, transcription of the medication order, and dosing instructions are accurate, and that total amounts of alcohol and propylene glycol from all concomitant medications are accounted for. Oral solution contains ethanol (42.4% v/v) and propylene glycol (15.3% w/v) [4].

Uses

Antiretroviral Management in the Newborn: Lopinavir/ritonavir plus a two-NRTI backbone is a preferred initial therapy regimen for HIV infection in patients with a postmenstrual age 42 weeks or more and postnatal age 14 days to less than 4 weeks. This regimen may also be used as an alternative regimen in patients 4 weeks or older [1]

Antiretroviral Regimens for Initial Therapy	
Age Range	Regimen
Preferred Regimens	
Birth to less than 14 days (footnote 1, 2)	Any weight: 2 NRTIs plus nevirapine
	2 kg or more: 2 NRTIs plus raltegravir (footnote 3)
14 days (and 2 kg or greater) to less than 4 weeks	2 NRTIs plus lopinavir/ritonavir (footnote 2)
	2 NRTIs plus raltegravir (footnote 3)

4 weeks or older (and 3 kg or greater) to less than 2 years	2 NRTIs plus dolutegravir (footnote 4)	
2 years (and 14 kg or greater) or older	2 NRTIs plus bictegravir (footnote 5)	
Alternative Regimens		
14 days to less than 3 years	2 NRTIs plus nevirapine (footnote 7)	
4 weeks to less than 3 months	Any weight: 2 NRTIs plus lopinavir/ritonavir (footnote 2)	
	2 kg or more: 2 NRTIs plus raltegravir (footnote 3)	
3 months to less than 3 years	2 NRTIs plus atazanavir/ritonavir	
	2 NRTIs plus lopinavir/ritonavir (footnote 2)	
	2 NRTIs plus raltegravir (footnote 3)	
3 years or older	2 NRTIs plus atazanavir/ritonavir	
	2 NRTIs plus darunavir/ritonavir (footnote 8)	
	2 NRTIs plus efavirenz (footnote 9)	
	2 NRTIs plus lopinavir/ritonavir (footnote 2)	
	25 kg or more	2 NRTIs plus elvitegravir/cobicistat (footnote 10)
	35 kg or more	2 NRTIs plus doravirine (footnote 11)
12 years or older with SMR 1 to 3	2 NRTIs plus one of the following: atazanavir/ritonavir, darunavir/ritonavir, efavirenz, lopinavir/ritonavir, raltegravir	
	25 kg or more	2 NRTIs plus elvitegravir/cobicistat
	35 kg or more	2 NRTIs plus one of the following: doravirine (footnote 11), rilpivirine (footnote 12), atazanavir/cobicistat
	40 kg or more	2 NRTIs plus darunavir/cobicistat
Preferred Dual NRTI Options for Use with Additional Drugs		

Birth to 1 month	abacavir plus lamivudine or emtricitabine (footnote 6)	
	zidovudine plus lamivudine or emtricitabine	
1 month to less than 2 years	abacavir plus lamivudine or emtricitabine (footnote 6)	
2 years or older and SMR 1 to 3	abacavir plus lamivudine or emtricitabine(footnote 6)	
	14 kg or greater and receiving a regimen that contains an INSTI or a NNRTI	emtricitabine/tenofovir alafenamide
	35 kg or greater and receiving a regiment that contains a boosted PI	
Alternative Dual NRTI Options for Use with Additional Drugs		
1 month to less than 6 years	zidovudine plus abacavir (footnote 6)	
	zidovudine plus lamivudine or emtricitabine	
2 years to 12 years	tenofovir disoproxil fumarate plus lamivudine or emtricitabine	
6 years or older and SMR 1 to 3	zidovudine plus abacavir (footnote 6)	
	zidovudine plus lamivudine or emtricitabine	

Footnotes:
1. Available clinical trial data do not suggest that initiating treatment within the first 14 days of life lead to better clinical outcomes than initiation after 14 days of age. Consult an expert in pediatric HIV infection before initiating in infants less than 14 days.
2. In general, lopinavir/ritonavir should not be administered to neonates before a postmenstrual age of 42 weeks and a postnatal age of 14 days or more.

3. Raltegravir film-coated tablets or chewable tablets can be used in children at least 2 years old. Consider use of the granules in infants from birth to 2 years. No dose recommendations are available for preterm infants or infants weighing less than 2 kg at birth.
4. Dolutegravir dispersible tablets can be administered in patients 4 weeks or older and 3 kg or greater. Dolutegravir film-coated tablets can be used in patients 14 kg or greater.
5. Only available as part of a fixed-dose combination tablet that contains bictegravir/emtricitabine/tenofovir alafenamide.
6. Abacavir is not approved by the FDA for use in full-term neonates and infants less than 3 months. Recent trial data from the IMPAACT P1106 trial and 2 observational cohorts provides reassurance on the safety of abacavir in patients less than 3 months. Before abacavir administration, a negative HLA-B 5701 allele test should be established
7. Do not use nevirapine in postpubertal girls if CD4 count is greater than 250/mm(3) unless clear benefit. Nevirapine is FDA-approved for infants 15 days or older.8. Darunavir should only be used in children 10 kg or more. Do not use darunavir once daily in children younger than 12 years or weighing less than 40 kg or if any one of the following resistance-associated substitutions are present: V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, and L89V.
8. Darunavir/ritonavir-boosted is an alternative recommendation for children 6 years to younger than 12 years and weighing greater than 25 kg because there are options that can be administered once-daily and that are better tolerated. Darunavir/ritonavir-boosted administered once daily is an option for adolescents 12 years or older and weighing at least 40 kg who are not sexually mature (SMR 1 to 3)
9. Efavirenz is not recommended as initial therapy for children 3 months to 3 years (weighing at least 3.5 kg), even though it's FDA approved for this age group. Available as part of fixed-dose combination tablets
10. Elvitegravir is currently recommended only in fixed-dose combination tablets. Tablets containing elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide are an alternative for children weighing at least 25 kg due to multiple drug-drug interactions with cobicistat and a lower barrier to the development of resistance to elvitegravir

11. Doravirine is not FDA approved for pediatric use. Based on data on the efficacy and tolerability of doravirine in adults, as well as early findings from PK studies, the Panel recommends doravirine as an alternative treatment option for patients 35 kg or more 12. Rilpivirine should only be administered to adolescents 12 years or older and weighing 35 kg or more who have an initial viral load of 100,000 copies/mL or less. Available as part of a fixed-dose combination products.
INSTIs: bictegravir, dolutegravir, elvitegravir, raltegravir
NRTIs: abacavir, emtricitabine, lamivudine, tenofovir alafenamide, tenofovir disoproxil fumarate, zidovudine
NNRTIs: doravirine, efavirenz, nevirapine, rilpivirine
PIs: atazanavir, darunavir, lopinavir, ritonavir
Key: INSTI = integrase strand transfer inhibitor, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, SMR = sexual maturity rating
Reference: https://clinicalinfo.hiv.gov /en/guidelines/pediatric-arv/whats-new April 2022

Pediatric FDA Approved Indications
Lopinavir/ritonavir is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in patients 14 days of age or older [4].

Administration

Administer with a feeding. Use a calibrated dosing syringe to administer the oral solution dose [4].
If coadministered with didanosine, give didanosine 1 hour before or 2 hours after lopinavir/ritonavir dose [4].
Oral solution not recommended for use with polyurethane feeding tubes due to ethanol and propylene glycol content and potential for incompatibility. Compatible feeding tubes include silicone and polyvinyl chloride (PVC) [5].

MEDICATION SAFETY

Contraindications/Precautions

CONTRAINDICATIONS

•Concomitant use with the following alpha 1-adrenoreceptor antagonist: Alfuzosin [8]
•Concomitant use with the following antianginal agent: Ranolazine [8]
•Concomitant use with the following antiarrhythmic agent: Dronedarone [8]
•Concomitant use with the following anti-gout agent: Colchicine [8]
•Concomitant use with the following antimycobacterial agent: Rifampin [8]
•Concomitant use with the following antipsychotics: Lurasidone, pimozide [8]
•Concomitant use with the following ergot derivatives: Dihydroergotamine, ergotamine, methylergonovine [8]
•Concomitant use with the following GI motility agent: Cisapride [8]
•Concomitant use with the following hepatitis C direct-acting antiviral agent: Elbasvir/grazoprevir [8]
•Concomitant use with the following herbal product: St. John's wort (Hypericum perforatum) [8]
•Concomitant use with the following HMG-CoA reductase inhibitors: Lovastatin, simvastatin [8]
•Concomitant use with the following microsomal triglyceride transfer protein (MTTP) inhibitor: Lomitapide [8]
•Concomitant use with the following phosphodiesterase type-5 (PDE5) inhibitor: Sildenafil (when used for the treatment of pulmonary arterial hypertension) [8]
•Concomitant use with the following sedative/hypnotic agents: Triazolam, oral midazolam [8]

PRECAUTIONS

Cardiovascular: Avoid use in patients with congenital long QT syndrome or hypokalemia, as QT interval prolongation and torsade de pointes have been reported [9].
Cardiovascular: PR interval prolongation and 2nd or 3rd degree atrioventricular block have been reported [9].
Cardiovascular: Underlying structural heart disease, conduction system abnormalities, ischemic heart disease, or cardiomyopathies; increased risk of conduction abnormalities [9]
Concomitant use: Avoid once-daily use with carbamazepine, efavirenz, nevirapine, nelfinavir, phenobarbital, or phenytoin [9].
Concomitant use: Avoid use with avanafil, boceprevir, rivaroxaban, salmeterol, simeprevir, tipranavir [10], amiodarone, or rifapentine [11].
Concomitant use: Avoid use with fluticasone or other glucocorticoids [9] , budesonide (systemic, inhaled, or intranasal), or prednisone [11] unless benefit outweighs risk of systemic corticosteroid side effects [11][9].
Concomitant use: Avoid use with QT interval-prolonging drugs [9].
Concomitant use: Avoid use with voriconazole unless benefit outweighs risk of decreased voriconazole efficacy [9].
Endocrine and metabolic: New onset diabetes mellitus, exacerbation of preexisting diabetes mellitus, hyperglycemia, and diabetic ketoacidosis have been reported with protease inhibitor use; consider monitoring for hyperglycemia and new onset or exacerbation of diabetes mellitus [7].
Endocrine and metabolic: Large elevations of triglycerides and cholesterol have been reported; monitoring recommended [9].
Gastrointestinal: Pancreatitis has been reported, especially in patients with marked triglyceride elevations and in patients with a history of pancreatitis [9].

Hematologic: Hemophilia type A or B; increased bleeding (eg, skin hematomas, hemarthrosis) has been reported [9]
Hepatic: New or worsening of transaminase elevations or hepatic decompensation may occur in patients with hepatitis B or C or with marked transaminase elevation; monitoring recommended [9]
Hepatic: Hepatic dysfunction, including some fatalities, has been reported; monitoring recommended [9].
Immunologic: Autoimmune disorders (eg, Graves disease, polymyositis, Guillain-Barre syndrome) have been reported in the setting of immune reconstitution and may occur many months after initiation of therapy [9].
Immunologic: Immune reconstitution syndrome may occur, leading to an inflammatory response in patients with indolent or residual opportunistic infections [9].
Preterm neonates: Use of the oral solution in preterm neonates in the immediate postnatal period is not recommended due to potential adverse effects caused by propylene glycol accumulation (complete AV block, bradycardia, cardiomyopathy, lactic acidosis, acute renal failure, CNS depression, and respiratory complications); if use is required, monitoring recommended [9].

Adverse Effects

Common, 6 months to 12 years: In a study of pediatric patients 6 months to 12 years of age (n=100), taste aversion (22%), vomiting (21%), and diarrhea (12%) were the most commonly reported events in patients treated for up to 48 weeks. Rash of moderate to severe intensity was reported in 3% of patients [4]. Other selected adverse events include gastrointestinal intolerance, nausea, and hyperlipidemia, especially hypertriglyceridemia, along with elevations in liver transaminases, hyperglycemia, PR interval prolongation, QT interval prolongation, and Torsades de Pointes.

Monitoring

[6]

<table>
<tr><td colspan="8">Antiretroviral Monitoring in Children (adjust schedule based on the specific antiretroviral regimen)</td></tr>
<tr><td rowspan="2"></td><td rowspan="2">Entry into Care†</td><td>ART Initiation ††</td><td>1 to 2 weeks after initiation</td><td>2 to 4 weeks after initiation</td><td>Every 3 to 4 months †††</td><td>Every 6 to 12 months ‡</td><td>Virologic Failure (Prior to switching ARV regimen)</td></tr>
<tr><td colspan="6">If clinical, immunologic, or virologic deterioration is suspected, perform more frequent CD4 cell count and plasma viral load monitoring. If toxicity noted, perform testing more frequently until toxicity resolved</td></tr>
</table>

Medical History and Physical Examination ‡‡, ‡‡‡	X	X	X	X	X		X
Adherence Evaluation ‡‡‡		X	X	X	X		X
CBC with differential †††	X	X		X	X		X
Chemistries †††, ♦♦	X	X		X	X		X
Lipid Panel ‡	X	X				X	
Random Plasma Glucose ♦♦♦		X				X	
Urinalysis	X	X				X	
CD4 count	X	X			X		X
Plasma Viral Load ♦	X	X		X	X		X
Resistance Testing	X						X
Hepatitis B screening ¶	X						X
Pregnancy Test for Girls and Young Women of Childbearing Potential	X	X					X
HLA-B*5701 ¶¶	X						

KEY: ARV = Antiretroviral; ART = Antiretroviral therapy; CBC = complete blood count

† If a child does not initiate ART after receiving an HIV diagnosis, the child's CD4 count and plasma viral load should be monitored at least every 3 to 4 months.

†† If ART is initiated within 30 to 90 days of a pre-therapy laboratory result, repeat testing may not be necessary.

††† CD4 cell count, CBC, and chemistries can be monitored less frequently (every 6 to 12 months) in children and youth who are adherent to therapy and have CD4 cell count values well above the threshold for opportunistic infection risk, have sustained viral suppression, and have stable clinical status for more than 2 to 3 years. Viral load testing every 3 to 4 months is generally recommended to monitor ARV adherence.

‡ If lipids have been abnormal in the past, more frequent monitoring

might be needed. For patients treated with TDF, more frequent urinalysis should be considered.
‡‡ Pay special attention to changes in weight that might occur after altering an ARV regimen. Weight gain or weight loss may occur when using some ARV drugs.
‡‡‡ Virtual visits may be appropriate at some times points, particularly for adherence assessments and for visits for established patients.
♦ Some experts monitor viral load more often (with each injection) in adolescents initiating injectable cabotegravir and rilpivirine (CAB and RPV). Viral load monitoring should be performed 4 to 8 weeks after switching to long-acting CAB and RPV. HIV-RNA also should be checked in patients with unplanned missed visits and delayed dosing of long-acting CAB and RPV. When viremia develops during long-acting therapy, resistance testing, including integrase resistance testing, should be performed. Follow-up dosing in patients with missed doses should not be delayed while waiting for viral load and resistance test results. However, regimen changes should be prompted if resistance to CAB and/or RPV is discovered.
♦♦ Refers to a comprehensive metabolic panel. Some experts perform a comprehensive panel at entry and routinely test Cr, ALT, AST, with additional tests tailored to the history of the individual patient
♦♦♦ Random plasma glucose is collected in gray-top blood collection tube or other designated tube. Some experts would consider monitoring HgbA1C, rather than blood glucose, in children at risk for prediabetes/diabetes.
¶ Only recommended for individuals who have previously demonstrated no immunity to HBV and who are initiating a regimen that contains ARV drugs with activity against HBV (ie, lamivudine, emtricitabine, tenofovir alafenamide, or tenofovir disoproxil fumarate).
¶¶ Conduct HLA-B*5701 on entry prior to initiating abacavir if not done previously. Choose an alternative ARV drug if the patient is HLA-B*5701 positive.

Reference: https://clinicalinfo.hiv.gov/en/guidelines/pediatric-arv/whats-new April 2023

CD4 Cell Count and Percentages in Healthy Children							
	0 to 3 months	3 to 6 months	6 to 12 months	1 to 2 years	2 to 6 years	6 to 12 years	12 to 18 years
CD4 cell count (footnote 1)	2600 (1600 to 4000)	2850 (1800 to 4000)	2670 (1400 to 4300)	2160 (1300 to 3400)	1380 (700 to 2200)	980 (650 to 1500)	840 (530 to 1300)
CD4 percentage (footnote 1)	52 (35 to 64)	46 (35 to 56)	46 (31 to 56)	41 (32 to 51)	38 (28 to 47)	37 (31 to 47)	41 (31 to 52)
1. Values presented as median (10th to 90th percentile)							
Reference: https://clinicalinfo.hiv.gov/en/guidelines /pediatric-arv/whats-new April 2023							

Consider monitoring for hyperglycemia or new onset or worsening diabetes mellitus during treatment with lopinavir/ritonavir [7].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Lopinavir inhibits the HIV protease and prevents cleavage of the Gag-Pol polyprotein, thus reducing the probability of viral particles reaching a mature, infectious state. Ritonavir is administered solely to increase lopinavir plasma levels. Tmax following oral administration of lopinavir/ritonavir is approximately 4 hours. Food increases bioavailability of oral solution; therefore, lopinavir/ritonavir oral solution should be administered with feedings. Protein binding is approximately 98% to 99% and is primarily to alpha-1-acid glycoprotein (higher affinity) and albumin. Lopinavir is extensively metabolized in the liver, primarily by the CYP3A4 enzyme system. Ritonavir is a potent inhibitor of CYP3A4 and inhibits the metabolism of lopinavir, thereby increasing lopinavir concentrations. There are many drug interactions with lopinavir involving CYP3A4. Approximately 2% and 20% of lopinavir is excreted unchanged in the urine and feces, respectively [4]. In HIV-infected infants less than 6 weeks of age (range, 3.6 to 5.9 weeks) receiving oral solution of lopinavir 300 mg/ritonavir 75 mg/m^2 twice daily, the mean elimination half life was 3.7 hours (range 2.1 to 5.8 hours; n=9), according to a prospective, phase I/II, open-label study [3]. A pharmacokinetic study showed that the clearance of lopinavir/ritonavir was dependent on weight and postmenstrual age in neonates and infants from birth to less than 2 years of age (weight range from 1.16 to 10.4 kg; n=96) [12].

ABOUT

Special Considerations/Preparation

Availability: Oral solution in a concentration of 80 mg lopinavir/20 mg ritonavir per mL that also contains 42.4% alcohol (v/v) and propylene glycol (15.3% w/v).
Storage: Preferably, store oral solution refrigerated. Refrigerated oral solution is stable until the expiration date printed on the label; if stored at room temperature up to 25 degrees C (77 degrees F), oral solution should be used within 2 months [4].

LORazepam

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

0.05 to 0.1 mg/kg per dose IV slow push. Repeat doses based on clinical response.

Uses

Anticonvulsant, acute management of patients with seizures refractory to conventional therapy.

Administration

Intravenous: For intermittent IV use, a concentration of 1 or 2 mg/mL should be infused at a rate not to exceed 2 mg per minute. Avoid intra-arterial administration and perivascular extravasation [1]. In neonates, it might be more practical to use concentrations such as 0.2 mg/mL or 0.4 mg/mL.

MEDICATION SAFETY

Contraindications/Precautions

Contraindications

- Intraarterial administration; may produce arteriospasm resulting in gangrene (injection) [2]
- Acute narrow-angle glaucoma [2][3][4]
- Premature infants; injection formulation contains benzyl alcohol [2]
- Respiratory insufficiency, severe; in the absence of resuscitative equipment (injection) [2][5]
- Sleep apnea syndrome (injection) [2][5]

Precautions

Access: Patients receiving concomitant therapy with benzodiazepines or CNS depressants should not be denied access to medication-assisted treatment drugs (eg, methadone and buprenorphine); if concomitant use is necessary, careful management and monitoring recommended [6].

Administration: Higher doses; increased risk of propylene glycol toxicity or polyethylene

glycol toxicity especially in patients with renal impairment (injection) [5][1]
Concomitant anesthesia: Risk of heavy sedation and possible airway obstruction (injection) [5][1]
Concomitant use of medications that lower the convulsive threshold (such as antidepressants): Increased risk of convulsions/seizures if lorazepam is abruptly withdrawn (oral) [7][4]
Hepatic: In patients with hepatic insufficiency, severe and/or encephalopathy; risk of worsening encephalopathy; consider dose adjustments (oral) [7][4]
Hepatic: Use is not recommended in patients with hepatic failure (injection) [5][1]
Neurologic: CNS depression may result in sedation that impairs the ability to perform tasks requiring mental alertness (eg, operating dangerous machinery including motor vehicles) [3].
Neurologic: Heavily sedated patients have an increased risk for airway obstruction (injection) [5][1]
Neurologic: Multiple doses increases the risk of impaired consciousness (injection) [5][1]
Neurologic: Patients with seizure disorder have an increased risk of convulsions/seizures if lorazepam is abruptly withdrawn (oral) [7][4]
Neurologic: Patients with status epilepticus have a risk of respiratory depression; monitoring is recommended (injection) [5][1]
Psychiatric: Paradoxical reactions have been reported [3][2], with increased risk in elderly and pediatric patients; consider discontinuation [3]
Psychiatric: Patients with primary depressive disorder or psychosis have a risk of suicide or exacerbation of depression; use is not recommended (oral) [7][4]
Psychiatric: Patients with significant personality disorders have an increased risk of drug dependence (oral) [7][4]
Renal: Use is not recommended in patients with renal failure (injection) [5][1]
Respiratory: Patients with compromised respiratory function (sleep apnea syndrome and chronic obstructive pulmonary disease) have an increased risk of respiratory depression (oral) [7][4]
Respiratory: Patients with limited pulmonary reserve have a risk of hypoventilation or hypoxic cardiac arrest (injection) [5][1]
Special Populations: Brain development in children may be affected by repeated or lengthy use of general anesthetic and sedation drugs during surgeries or procedures, especially in children younger than 3 years or in fetuses of pregnant women during the third trimester; balance appropriate anesthesia use and timing of elective procedures that can be delayed against potential risks in children younger than 3 years and pregnant women, particularly with procedures that are longer than 3 hours or multiple procedures [8][9].
Special populations: Debilitated patients have an increased risk of hypoventilation, or hypoxic cardiac arrest (injection) [5][1]; and increased risk of sedation (oral); initial oral dose should not exceed 2 mg, monitoring recommended, consider dose adjustment [7][4]
Special populations: Neonate patients have an increased risk of fatal "gasping syndrome" with injection due to benzyl alcohol, especially with higher doses [8][5] and in premature or low-birth-weight infants [8]
Special populations: Pediatric patients have an increased incidence of sensitivity to benzyl alcohol, polyethylene glycol, and propylene glycol especially in high doses (injection) [5][1]
Special populations: Seizure activity and myoclonus have been reported in premature and low-birth-weight infants (injection) [5][1]
Withdrawal: A protracted withdrawal syndrome with symptoms lasting weeks to more than 12 months has been reported in benzodiazepine users [3][2]

Adverse Effects

Respiratory depression. Rhythmic myoclonic jerking has occurred in premature neonates receiving LORazepam for sedation.

Black Box Warning

Injection Solution
Risks From Concomitant Use With Opioids; Abuse, Misuse, and Addiction; and Dependence and Withdrawal Reactions:[2]

- Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of these drugs in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation.
- The use of benzodiazepines, including lorazepam injection, exposes users to risks of abuse, misuse, and addiction, which can lead to overdose or death. Abuse and misuse of benzodiazepines commonly involve concomitant use of other medications, alcohol, and/or illicit substances, which is associated with an increased frequency of serious adverse outcomes. Before prescribing lorazepam injection and throughout treatment, assess each patient's risk for abuse, misuse, and addiction.
- The continued use of benzodiazepines for several days to weeks may lead to clinically significant physical dependence. The risks of dependence and withdrawal increase with longer treatment duration and higher daily dose. Although lorazepam injection is indicated only for intermittent use, if used more frequently than recommended, abrupt discontinuation or rapid dosage reduction of lorazepam injection may precipitate acute withdrawal reactions, which can be life-threatening. For patients using lorazepam injection more frequently than recommended, to reduce the risk of withdrawal reactions, use a gradual taper to discontinue lorazepam injection.

Oral Tablet
Risks From Concomitant Use With Opioids; Abuse, Misuse, and Addiction; and Dependence and Withdrawal Reactions:[3]

- Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of these drugs for patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation.
- The use of benzodiazepines, including lorazepam, exposes users to risks of abuse, misuse, and addiction, which can lead to overdose or death. Abuse and misuse of benzodiazepines commonly involve concomitant use of other medications, alcohol, and/or illicit substances, which is associated with an increased frequency of serious adverse outcomes. Before prescribing lorazepam and throughout treatment, assess each patient's risk for abuse, misuse, and addiction.
- The continued use of benzodiazepines, including lorazepam may lead to clinically significant physical dependence. The risks of dependence and withdrawal increase with longer treatment duration and higher daily dose. Abrupt discontinuation or rapid dosage reduction of lorazepam after continued use may precipitate acute withdrawal reactions,

which can be life-threatening. To reduce the risk of withdrawal reactions, use a gradual taper to discontinue lorazepam or reduce the dosage.

Solution Compatibility

D_5W, NS, and sterile water for injection.

Terminal Injection Site Compatibility

Acyclovir, amikacin, amiodarone, bumetanide, cefepime, cefotaxime, cimetidine, dexamethasone, dobutamine, dopamine, epinephrine, erythromycin lactobionate, famotidine, fentanyl, fluconazole, fosphenytoin, furosemide, gentamicin, heparin, hydrocortisone succinate, labetalol, levetiracetam, linezolid, methadone, metronidazole, midazolam, milrinone, morphine, nicardipine, nitroglycerin, pancuronium bromide, piperacillin, piperacillin-tazobactam, potassium chloride, propofol, ranitidine, remifentanil, trimethoprim-sulfamethoxazole, vancomycin, vecuronium, and zidovudine.

Terminal Injection Site Incompatibility

Fat emulsion. Aztreonam, caffeine citrate, and imipenem/cilastatin.

Monitoring

Monitor respiratory status closely. Observe IV site for signs of phlebitis or extravasation.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Dose-dependent CNS depression. Onset of action within 5 minutes; peak serum concentration within 45 minutes. Duration of action is 3 to 24 hours. Mean half-life in term neonates is 40 hours. Metabolized to an inactive glucuronide, which is excreted by the kidneys. Highly lipid-soluble.

ABOUT

Special Considerations/Preparation

Injection available in 2-mg/mL and 4-mg/mL concentrations (1-mL preservative-free vial and 10-mL multidose vials) [1].

Limited data are available for neonates. Some available products contain 2% (20 mg/mL) benzyl alcohol and 18% polyethylene glycol 400 in propylene glycol. For intermittent IV use, must be diluted with an equal volume of compatible diluent; resultant concentration is 1 mg/mL and 2 mg/mL for the 2 mg/mL and 4 mg/mL concentrations, respectively [1] One possible concentration for ease of measuring a dose would be 0.4 mg/mL; prepare by adding 1 mL of 4 mg/mL concentration in 9 mL of preservative-free sterile water for injection. In products that contain benzyl alcohol, use of the 4 mg/mL vial will reduce the amount of benzyl alcohol per dose compared with the 2 mg/mL vial.
Solutions should not be used if they are discolored or contain a precipitate.

Lucinactant

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Respiratory Distress Syndrome; Prophylaxis
5.8 mL/kg birth weight intratracheally in 4 equal aliquots (with infant repositioned between each aliquot). Up to 4 doses may be given in the first 48 hours of life. Give no more frequently than every 6 hours[1] to 12 hours, unless surfactant is being inactivated by an infectious process, meconium, or blood [2]. Administer prophylactic lucinactant after initial resuscitation but within 10 to 30 minutes after birth [2][3][4].

Uses

Prevention of respiratory distress syndrome (RDS) in premature infants: Routine continuous positive airway pressure (CPAP) is considered superior to prophylactic surfactant therapy. It is strongly recommended that CPAP immediately after birth with subsequent selective surfactant administration be considered as an alternative to routine intubation with prophylactic or early surfactant administration in preterm infants [2].
Lucinactant reduced the occurrence of RDS among premature neonates (32 weeks gestational age or younger) at high risk for developing RDS more effectively than colfosceril palmitate (47.2% vs 39.1%; p=0.005) and also reduced the number of RDS-related deaths compared with colfosceril palmitate and beractant treatment groups (4.7% vs 9.4% (p=0.002) vs 10.5% (p=0.001), respectively) in a multicenter, randomized comparison trial (n=1294) [4]. Lucinactant and poractant alfa were similar in terms of efficacy in premature infants (24 to 28 weeks gestation) at high risk for developing RDS in a multicenter randomized noninferiority trial (n=252). The rate of survival without BPD at 28 days (primary outcome) was 37.8% vs 33.1%, respectively [3]. In a one-year follow-up of these 2 studies (n=1546), lucinactant had similar efficacy to the animal-derived and synthetic exogenous surfactant products for decreasing mortality and morbidity rates in premature neonates at risk for RDS. Neurologic function was similar in infants who received lucinactant and those that received other surfactants [5].

Meconium aspiration syndrome: Infants (gestational age, 35 weeks or more) treated with lucinactant lavage within 72 hours of birth, compared with no lavage, experienced more rapid and more sustained improvement in oxygenation and shorter ventilation times (median 4.6 vs 7.6 days); however, these outcomes were not statistically significant in an open-label, randomized trial (n=22). Lucinactant (2.5 mg/mL) 8 mL/kg per lung was instilled over approximately 20 seconds followed by suctioning after 5 ventilator breaths. This was repeated followed by a third treatment of lucinactant (10 mg/mL) 8 mL/kg per lung and suctioned at the discretion of the physician [6].

Pediatric FDA Approved Indications

Lucinactant intratracheal suspension is indicated for the prevention of respiratory distress syndrome (RDS) in premature infants at high risk for RDS [1].

Administration

Preparation

Prior to administration, warm the lucinactant intratracheal suspension vial for 15 minutes in a preheated dry block heater set at 44 degrees C (111 degrees F). Remove the vial from the heater and shake vigorously until the suspension is uniform and free-flowing. After withdrawn into a syringe for administration, the temperature of the suspension will be about 37 degrees C (99 degrees F). Warmed vials should not be refrigerated after warming but may be stored in the carton at room temperature for no more than 2 hours [1].

Administration

For intratracheal administration only. Using a 16- or 18-gauge needle, slowly draw up the dose of warmed and vigorously shaken lucinactant intratracheal suspension into an appropriately sized syringe [1].

Before administration of the suspension, ensure patency and proper placement of the endotracheal tube. The endotracheal tube may be suctioned before lucinactant administration if necessary. Allow the infant to stabilize before administration [1].

The infant should be positioned in the right lateral decubitus position with head and thorax at a 30 degree upward inclined position. A 5-French end-hole catheter with the syringe of lucinactant attached should be threaded through a Bodai valve (or equivalent device) to allow maintenance of positive end-expiratory pressure. The tip of the catheter should be advanced into the endotracheal tube and positioned so that it is slightly distal to the end of the endotracheal tube [1].

The lucinactant dose should be delivered in 4 equal aliquots (each aliquot equal to one-fourth of the total dose). Administer the first aliquot while continuing positive pressure mechanical ventilation and maintaining a positive end-expiratory pressure of 4 to 5 cm Hg_2O. Adjust ventilator settings as necessary to maintain appropriate oxygenation and ventilation until the infant is stable (oxygen saturation of at least 90% and heart rate greater than 120 beats/minute) [1].

Maintain adequate positive pressure ventilation, move the infant to the left decubitus position, and repeat the administration procedure for the second aliquot. Pause between administration of each aliquot to evaluate the infant's respiratory status. Move the infant to the right decubitus position for administration of the third aliquot, and to the left decubitus position for administration of the fourth aliquot [1].

Remove the catheter after administration of the fourth aliquot, and resume usual ventilator management. Keep the head of the infant's bed elevated at least 10 degrees for at least 1 to 2 hours. Unless the infant develops significant airway obstruction, do not suction the infant for the first hour after dosing [1].

MEDICATION SAFETY

Contraindications/Precautions

Bradycardia, hypoxemia, airway obstruction, and reflux of drug into the endotracheal tube (ETT) may occur; if reactions occur, interrupt treatment until resolved. Suctioning of the ETT or reintubation may be necessary for persistent airway obstruction. Respiratory status may change rapidly with administration; monitoring recommended, oxygen and ventilatory support modifications may be required [1].

Adverse Effects

Bradycardia, hypoxemia, airway obstruction, and reflux of drug into the endotracheal tube are common adverse events. In clinical trials, rates of bradycardia and oxygen desaturation have ranged from 3% to 23% and 8% to 58%, respectively. Endotracheal tube reflux occurred at an incidence of 18% to 27% [1][7]. The incidence of pulmonary hemorrhage, pulmonary leaks, patent ductus arteriosus, sepsis, intraventricular hemorrhage, necrotizing enterocolitis (grade 2 or higher), retinopathy of prematurity (grade 3 or 4), and periventricular leukomalacia was not significantly different between lucinactant and the comparators in clinical trials [4][3].
Gagging (20%) and coughing (27%) occurred in infants (gestational age, 35 weeks or more) treated with lucinactant lavage within 72 hours of birth. Oxygen desaturation, probably related to lavage therapy, occurred in 1 infant with herpes simplex virus infection [6].

Monitoring

Monitor oxygen saturation and ventilatory support frequently and modify according to changes in respiratory status [1].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Lucinactant is a synthetic, non-pyrogenic pulmonary surfactant which acts like endogenous surfactant by restoring surface activity to the lung of premature infants deficient in pulmonary surfactant. It consists of phospholipids, a fatty acid, and sinapultide (21-amino acid synthetic peptide). No pharmacokinetic data are available regarding the absorption, distribution, metabolism, or elimination of lucinactant [1].

ABOUT

Special Considerations/Preparation

Available as an intratracheal suspension containing 8.5 mL in a glass vial. Each mL contains 30 mg phospholipids (22.50 mg dipalmitoylphosphatidylcholine and 7.50 mg palmitoyloleoyl-phosphatidylglycerol, sodium salt), 4.05 mg palmitic acid, and 0.862 mg sinapultide. Contains no preservatives; single-use vials only. Store in refrigerator and protect from light; do not freeze [1].

Prior to administration, warm the lucinactant intratracheal suspension vial for 15 minutes in a preheated dry block heater set at 44 degrees C (111 degrees F). Remove the vial from the heater and shake vigorously until the suspension is uniform and free-flowing. After withdrawn into a syringe for administration, the temperature of the suspension will be about 37 degrees C (99 degrees F). Warmed vials should not be refrigerated after warming but may be stored in the carton at room temperature for no more than 2 hours [1].

Magnesium sulfate

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Resuscitation (Pulseless Torsades)
25 to 50 mg/kg IV/intraosseous rapid infusion (over several minutes) [1][2].

Hypomagnesemia
25 to 50 mg/kg IV infusion over 10 to 20 minutes [1]

Daily Maintenance Requirements (Parenteral Nutrition)
0.25 to 0.5 mEq/kg/day IV [3][4].

Uses

Treatment of **torsades de pointes** (polymorphic ventricular tachycardia associated with long QT interval) [1][6]. The American Heart Association (AHA) did not review the use of magnesium in the 2015 Neonatal Resuscitation guidelines; therefore, the 2010 AHA guidelines still apply [7]

Treatment and prevention of **hypomagnesemia**[8][4].

Administration

Must be diluted prior to IV administration to a concentration of 200 mg/mL or less [5]. Give by rapid infusion (over several minutes) for torsades, and over 10 to 20 minutes for hypomagnesemia [1].

MEDICATION SAFETY

Contraindications/Precautions

Contraindicated in patients with heart block or myocardial damage. Hypotension and bradycardia may occur with rapid infusion. Calcium chloride should be available to reverse magnesium toxicity. Use with caution in patients with renal impairment since magnesium sulfate is eliminated renally. Respiratory depression may occur from high magnesium levels.

Contains aluminum which may be toxic, especially in premature neonates and patients with renal impairment [8].

Adverse Effects

Flushing, sweating, hypothermia, and stupor may occur [8].
Low calcium levels or bone problems, including osteopenia or fractures, may occur in developing baby or fetus following prolonged use (greater than 5 to 7 days) of magnesium sulfate for stopping pre-term labor in pregnant mothers [10].

Solution Compatibility

D_5W, NS, and LR

Solution Incompatibility

Fat emulsion.

Terminal Injection Site Compatibility

Acyclovir, amikacin, ampicillin, aztreonam, cefazolin, cefotaxime, cefoxitin, chloramphenicol, clindamycin, dobutamine, enalaprilat, erythromycin lactobionate, esmolol, famotidine, gentamicin, heparin sodium, hydrocortisone sodium succinate, insulin, linezolid, meropenem, metoclopramide, metronidazole, micafungin, milrinone, morphine, nafcillin, nicardipine, ondansetron, oxacillin, penicillin G potassium, piperacillin, piperacillin/tazobactam, potassium chloride, propofol, sodium nitroprusside, tobramycin, trimethoprim/sulfamethoxazole, and vancomycin.

Terminal Injection Site Incompatibility

Amiodarone, amphotericin B, calcium chloride, cefepime, pantoprazole, and sodium bicarbonate.

Monitoring

Monitor serum and urinary magnesium levels [9][8]. Assess other electrolytes (calcium, potassium, phosphorus) and renal function periodically.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Magnesium is a cation of the intracellular fluid that is necessary for the activity of many enzyme systems and plays an important role in neurochemical transmission and muscular excitability. Approximately 99% of total body magnesium is in the intracellular compartment (bone, 85%; soft tissue and liver, 14%) and only 1% is present in the extracellular fluid. Because of this, serum concentrations do not adequately reflect total body magnesium stores. Most of the filtered magnesium (95%) is reabsorbed by the kidney. Magnesium deficiency leads to varied structural and functional abnormalities [9][8].
Signs of hypomagnesemia include tetany, cardiac arrhythmia, decreased bone stability, apathy, and increased susceptibility to epileptic seizures. Magnesium deficiency is associated with hypocalcemia, hypokalemia, hypophosphatemia, decreased urinary magnesium and calcium levels, and decreased magnesium levels in cerebrospinal fluid, bone, muscle, and hematopoietic cells [11][12].

ABOUT

Special Considerations/Preparation

Supplied as 50% concentration in 2-, 10-, and 50-mL single dose vials containing 500 mg/mL of magnesium sulfate which provides 4.06 mEq each of magnesium and sulfate. Osmolarity is 4.06 mOsm/mL; pH range of 5.5 to 7 [8][13].

DOSING/ADMINISTRATION

Dose

Prior to use, evaluate renal, cardiac, and pulmonary status of the patient and correct fluid and electrolyte imbalances, especially in patients with renal dysfunction [1].
Preterm and term neonates may be at higher risk for fluid and electrolyte abnormalities following mannitol administration due to decreased glomerular filtration rate and limited ability to concentrate urine [1].

The total dosage, concentration, and rate of administration depend on the age, weight, and condition of the patient being treated, including fluid requirement, electrolyte balance, serum osmolality, urinary output, and concomitant therapy [1].

Elevated Intracranial Pressure
0.25 g/kg IV over 30 minutes; may repeat every 6 to 8 hours [1].
Monitor during and following infusion and discontinue if renal, cardiac, or pulmonary status worsens or CNS toxicity develops [1].

Elevated Intraocular Pressure
1.5 to 2 g/kg of a 20% w/v solution (7.5 to 10 mL/kg) or as a 15% w/v solution (10 to 13 mL/kg) as a single dose IV over at least 30 minutes; when used preoperatively, administer 60 to 90 minutes prior to surgery [1].

Uses

Pediatric FDA Approved Indications
Intravenous
•Reduction of intracranial pressure and treatment of cerebral edema [1].
•Reduction of high intraocular pressure [1]

Administration

Injection:
•For IV infusion, preferably into a central vein [1].
•Do not administer simultaneously with blood products through the same administration set because of the possibility of pseudoagglutination or hemolysis [1].
•Use administration sets with a final in-line filter because of potential for crystals to form [1].
•Use a non-vented infusion set or close the vent on a vented set, avoid multiple connections,

and do not connect flexible containers in series to prevent air embolism [2]
•Fully evacuate residual gas in the container prior to administration and do not pressurize the flexible container to increase flow rates to prevent air embolism [2]
•If administration is controlled by a pumping device, turn off pump before the container runs dry to prevent air embolism [2]
•For single use only. Discard unused portion [1].

MEDICATION SAFETY

Contraindications/Precautions

Contraindications
IV formulation [1]
- Anuria
- Severe hypovolemia
- Active intracranial bleeding, except during craniotomy
- Preexisting severe pulmonary vascular congestion or pulmonary edema

Precautions
Intravenous
Administration: Peripheral venous irritation, including phlebitis, can occur when concentrations of 10% or greater are used [1]
Administration: Severe infusion site reactions (eg, compartment syndrome and swelling associated with extravasation) can occur [1]
Cardiovascular: Hypervolemia may occur and can lead to or exacerbate existing congestive heart failure; increased risk with accumulation of mannitol due to insufficient renal excretion [1]
Cardiovascular: Osmotic diuresis due to mannitol may cause or worsen dehydration/hypovolemia and hemoconcentration; hyperosmolarity may also occur [1]
Cardiovascular: Fluid and electrolyte imbalance (eg, hypernatremia, hyponatremia, hypokalemia, hyperkalemia, and metabolic acidosis/alkalosis), including severe and potentially fatal imbalances, may occur; increased risk in pediatric patients younger than 2 years, particularly preterm and term neonates; monitoring recommended and discontinuation may be required [1]
Concomitant use: with neurotoxic and nephrotoxic drugs (eg, aminoglycosides) or other diuretics should be avoided, if possible [1]
Endocrine and metabolic: Hyponatremia, new-onset or exacerbation, may occur [1]
Immunologic: Serious hypersensitivity reactions, including anaphylaxis, hypotension, and dyspnea resulting in cardiac arrest and death, have been reported with mannitol injection; if hypersensitivity reaction occurs, stop infusion immediately [2]
Neurological: CNS toxicity (eg, confusion, lethargy, coma) has been reported with some cases resulting in fatalities; monitoring recommended and discontinuation of therapy may be necessary [1]
Neurologic: At high concentrations, mannitol may cross the blood brain barrier and interfere with the ability of the brain to maintain the pH of the cerebrospinal fluid especially in the

presence of acidosis [1]
Neurologic: Preexisting compromise of the blood brain barrier; increased risk of increasing cerebral edema (general and focal) associated with repeated or continued use [1]
Neurologic: Rebound increase in intracranial pressure may occur several hours after infusion; increased risk in patients with compromised blood brain barrier [1]
Renal: Renal complications, including irreversible renal failure, have been reported; discontinuation may be required [2]
Renal: Reversible, oliguric acute kidney injury (AKI) has occurred in patients with normal renal function who received large IV doses; patients with oliguric AKI who develop anuria during therapy have increased risk of congestive heart failure, pulmonary edema, hypertensive crisis, coma, and death; monitor during and following administration; discontinuation may be required [2]
Renal: Osmotic nephrosis can occur with potential to lead to chronic or end-stage renal failure; increased risk with preexisting renal disease or concomitant use of nephrotoxic agents and other diuretics; monitoring recommended [1]
Renal: Urine output, inadequate; during infusion could lead to water intoxication or congestive heart failure; monitoring recommended and infusion suspension may be necessary [1]

Adverse Effects

Common: Hypersensitivity reactions, renal failure, CNS toxicity, hypo/hypervolemia, hypo/hypernatremia, hypo/hyperkalemia, and infusion site reactions [1].

Monitoring

Intravenous:[2]
•Monitor for hypersensitivity reactions during and following infusion, including laboratory tests for changes in fluid and electrolyte status [1].
•Closely monitor renal function, especially in patients with renal disease, conditions that put them at high risk for renal failure, or those receiving potentially nephrotoxic drugs or other diuretics [1].

- **Monitor during and after reduction of Intracranial pressure:**
- Serum osmolarity
- Fluid and serum electrolytes, including sodium, potassium, calcium, and phosphate
- Acid base balance
- Osmol gap
- Signs of hypovolemia and hypervolemia, including urine output
- Renal function
- Cardiac function
- Pulmonary function

- Intracranial pressure

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Intravenous mannitol is confined to the extracellular space and rapidly excreted by the kidney. Three hours after administration, approximately 80% of a 100-g dose is recovered in the urine. Mannitol is not secreted by tubular cells; it is freely filtered by the glomeruli, with less than 10% tubular reabsorption. Glomerular filtrate osmolarity elevation, and resulting interference with tubular reabsorption of water, induces diuresis. Sodium and chloride excretion is also increased by this process [3].

ABOUT

Special Considerations/Preparation

Intravenous: 5%, 10%, 15%, and 20% solution in flexible containers, and 25% flip-top 50-mL vial (all single-dose) [1][3].
Admixing with other medications is not recommended [1].
Inspect for crystals prior to use; if crystals are visible re-dissolve by warming solution up to 70 degrees C, with agitation. Do not heat in water or a microwave oven due to potential for product contamination or damage. Allow solution to cool to room or body temperature before reinspection for crystals and use [1].
Dissolve crystals in the flip-top vial by warming bottle in hot water at 80 degrees C; periodically shake vigorously. The 25% concentration may be autoclaved at 121 degrees C for 20 minutes at 15 psi. Do not place 25% mannitol injection in polyvinylchloride bags; a white flocculent precipitate may form from contact with PVC surfaces [3].

MCT Oil

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Medium Chain Triglyceride Oil

Medium chain triglycerides (MCT) are lipid fractions of coconut oil consisting of triglycerides with chain lengths of 6 to 10 carbons. Used to supplement orally, or added to tube feeding formulas. Mixes easily with enteral formulas.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Osmolality (mOsm/kg water): Not Available

Supplied: 1 quart glass bottles.

Ingredients: Medium chain triglycerides.

MCT Oil			
Nutrient	**per mL**	**per 15 mL (1 tbsp)**	**per 89 mL (3 fl oz)**
Calories	7.7	115	685.3
Protein, g	0	0	0
Fat, g	0.94	14	44.5
Carbohydrate, g	0	0	0
Water, g	0	0	0
Linoleic Acid, g	0.367	5.5	32.63

Fatty Acid Distribution	
Shorter than carbon 8	<6%
Caprylic C8:0	67%
Capric C10:0	23%
Longer than C10:0	<4%

ABOUT

Special Considerations/Preparation

For oral use only. Do not give parenterally (IV). Use within 60 to 90 days after a bottle is opened. Do not store in plastic container. MCT may break or soften plastic containers.

Meropenem

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Anthrax; meningitis or disseminated infection and meningitis cannot be ruled out (as part of a triple therapy regimen) [1]
32 weeks gestational age to full-term
0 to 1 week: 20 mg/kg/dose IV every 8 hours
1 to 4 weeks : 30 mg/kg/dose IV every 8 hours
Duration: 2 to 3 weeks or more until stable. Continue antimicrobial course of prophylaxis (usually oral therapy) for up to 60 days from onset of illness [1].

Anthrax; meningitis ruled out (as part of a combination regimen) [1]
32 to 34 weeks gestational age
0 to 1 week: 13 mg/kg/dose IV every 8 hours
1 to 4 weeks: 20 mg/kg/dose IV every 8 hours
34 weeks gestational age or older
0 to 4 weeks: 20 mg/kg/dose IV every 8 hours
Duration: 2 to 3 weeks or more until stable. Continue antimicrobial course of prophylaxis (usually oral therapy) for up to 60 days from onset of illness [1].

Intra-abdominal and non-CNS infections
Less than 32 weeks GA and less than 14 days PNA: 20 mg/kg IV every 12 hours [2][3][4].
Less than 32 weeks GA and 14 days PNA and older: 20 mg/kg IV every 8 hours [2][3][4].
32 weeks GA and older, and less than 14 days PNA: 20 mg/kg IV every 8 hours [2][3][4].
32 weeks GA and older, and 14 days PNA and older: 30 mg/kg IV every 8 hours [2][3][4].
Consider concomitant use of an aminoglycoside antibiotic [3].

Meningitis, Bacterial
Data regarding appropriate dosing for CNS infections are lacking [4]. Consider 40 mg/kg/dose at the recommended age-specific dosing interval [5][6]
Less than 32 weeks GA and less than 14 days PNA: every 12 hours [4].
Less than 32 weeks GA and 14 days PNA and older: every 8 hours [4].
32 weeks GA and older: every 8 hours [4].

Uses

Anthrax[1]:

Systemic Anthrax when meningitis can be ruled out (IV)
Combination IV Therapy

- **Preferred:** Ciprofloxacin. *Alternatives in order of preference: meropenem, levofloxacin, imipenem/cilastatin, or vancomycin. If strains are penicillin-susceptible, then penicillin G (preferred) or ampicillin (alternative).*
- **Plus**
- **Preferred:** Clindamycin. *Alternatives in order of preference: linezolid, doxycycline (not for neonates 37 weeks gestation or younger), or rifampin.*

Systemic Anthrax (meningitis or disseminated infection and meningitis cannot be ruled out) (IV)
Triple IV Therapy

- **Preferred:** Ciprofloxacin. *Alternatives in order of preference: levofloxacin or moxifloxacin*
- **Plus**
- **Preferred:** Meropenem. *Alternatives in order of preference: imipenem/cilastatin or doripenem. If strains are penicillin-susceptible, then penicillin G (preferred) or ampicillin (alternative).*
- **Plus**
- **Preferred:** Linezolid. *Alternatives in order of preference: clindamycin or rifampin or as a last resort, chloramphenicol*

Intra-abdominal infections, suspected or complicated [3], or other serious infections caused by susceptible Gram-negative organisms resistant to other antibiotics [15][16][17]. May be useful in treating neonates with meningitis, however, data are lacking.

Pediatric FDA Approved Indications
Complicated skin/skin structure infections due to *Staphylococcus aureus* (methicillin-susceptible isolates only), *Streptococcus pyogenes*, *S agalactiae*, viridans group streptococci, *Enterococcus faecalis* (vancomycin-susceptible isolates only), *Pseudomonas aeruginosa*, *Escherichia coli*, *Proteus mirabilis*, *Bacteroides fragilis*, and *Peptostreptococcus* species in pediatric patients 3 months and older [7].
Intra-abdominal infections [18] including complicated appendicitis and peritonitis caused by viridans group streptococci, *E coli*, *Klebsiella pneumoniae*, *P aeruginosa*, *B fragilis*, *B thetaiotaomicron*, and *Peptostreptococcus* species in pediatric patients 3 months and older [7]. Meropenem is considered an appropriate single agent for pediatric patients with a complicated extra-biliary intra-abdominal infection [18]
Bacterial meningitis caused by *S pneumoniae* (penicillin-susceptible isolates), *Haemophilus influenzae* , and *Neisseria meningitidis* in pediatric patients 3 months and older [7].

Administration

Administer as an IV infusion over 30 minutes [4] at a concentration of 1 to 20 mg/mL [7] .

Recommended standard concentrations are 20 and 50 mg/mL [8].
Prolonged Infusion: There are some data that promote prolonged infusions (e.g. over 4 hours) [9] particularly for resistant organisms in neonates [10]. In contrast, infusions of 20 mg/kg over 30 minutes were demonstrated pharmacokinetically to be adequate for very low birth weight infants [11]. Stability of meropenem needs to be considered as it is dependent on diluent, concentration, and temperature [7]. Some studies demonstrated longer stability times [12][13][14].

MEDICATION SAFETY

Contraindications/Precautions

Contraindications

Contraindicated in patients with known hypersensitivity to carbapenems or previous anaphylactic reactions to beta-lactams. Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving therapy with beta-lactams; these reactions are more likely to occur in those with a history of hypersensitivity to other beta-lactams or to multiple allergens. Before initiating therapy, obtain a detailed history of previous hypersensitivity reactions [19].

Precautions

Concomitant use: Coadministration with valproic acid or divalproex sodium is generally not recommended due to a reduction in valproic acid concentrations that may not respond to a dose increase. In patients with well-controlled seizures on valproic acid or divalproex sodium, antibiotics other than carbapenems are recommended, and if coadministration of meropenem is necessary, supplemental anticonvulsant therapy is recommended [19]
Dermatologic: Severe cutaneous adverse reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, erythema multiforme, and acute generalized exanthematous pustulosis have been reported; if signs and symptoms appear, immediately withdraw therapy and consider an alternative [20].
Neurological: Seizures and other CNS adverse events have been reported with meropenem therapy; these occurred mainly in patients with CNS disorders (eg, brain lesions or history of seizures) or patients with bacterial meningitis and/or compromised renal function [19].

Adverse Effects

Meropenem was studied in infants younger than 91 days with suspected or confirmed intra-abdominal infections. Dosages were as follows: Gestational age (GA) less than 32 weeks and postnatal age (PNA) less than 14 days were treated with meropenem 20 mg/kg IV every 12 hours (group 1, n=39), GA less than 32 weeks and PNA 14 days or greater were treated with 20 mg/kg IV every 8 hours (group 2, n=103), GA 32 weeks or greater and PNA less than 14 days were treated with 20 mg/kg IV every 8 hours (group 3, n=31), and GA 32 weeks or greater and PNA 14 days or greater were treated with 30 mg/kg IV every 8 hours (group 4,

n=27) [3].
Common: Sepsis (6%), seizures (5%), elevated conjugated bilirubin (5%), hypokalemia (5%). Among all reported adverse events, those thought to be possible related to meropenem included coagulopathy, spontaneous ileal perforation, extravasation, fungal skin infection, elevated triglycerides, hypoglycemia, osteopenia, skin breakdown, rash (reported in 1 patient each), elevated SCr or acute renal failure, hypotension (reported in 2 patients each), sepsis (3 patients), elevated direct bilirubin (4 patients), seizures (7 patients) [3].
Seizures: Reported in 10 participants; none were thought to be caused by meropenem; half of those with seizures had a CNS condition that could cause seizures [3].

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Aminophylline, atropine, caspofungin, cimetidine, dexamethasone, digoxin, dobutamine, dopamine, enalaprilat, fluconazole, furosemide, gentamicin, heparin, insulin, linezolid, metoclopramide, milrinone, morphine, norepinephrine, phenobarbital, potassium chloride, ranitidine, and vancomycin.

Terminal Injection Site Incompatibility

Acyclovir, amphotericin B, calcium gluconate, metronidazole, sodium bicarbonate, and zidovudine.

Monitoring

Periodic CBC (for thrombocytosis and eosinophilia) and hepatic transaminases. Assess IV site for signs of inflammation.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action: Meropenem is a broad-spectrum carbapenem antibiotic that

penetrates well into the CSF and most body tissues. It exhibits time-dependent killing of gram-negative and gram-positive pathogens, and the goal of therapy is to keep free drug concentrations above the MIC for at least 40% of the dosing interval. It is relatively stable to inactivation by human renal dehydropeptidase. [21].

Meropenem multiple-dose pharmacokinetics were studied in infants younger than 91 days with suspected or confirmed intra-abdominal infections. Dosages were as follows: Gestational age (GA) less than 32 weeks and postnatal age (PNA) less than 14 days were treated with meropenem 20 mg/kg IV every 12 hours (group 1, n=39), GA less than 32 weeks and PNA 14 days or greater were treated with 20 mg/kg IV every 8 hours (group 2, n=103), GA 32 weeks or greater and PNA less than 14 days were treated with 20 mg/kg IV every 8 hours (group 3, n=31), and GA 32 weeks or greater and PNA 14 days or greater were treated with 30 mg/kg IV every 8 hours (group 4, n=27) [4].
Target plasma concentrations: Greater than 4 mcg/mL for 50% of the dosing interval achieved by 96.3%; greater than 2 mcg/mL for at least 75% of the interval achieved by 92% [4]
Vd: Negatively associated with albumin
Distribution into CSF: 70% penetration; concentrations ranged from 0.7 to 34.6 mcg/mL (9 samples) [4]
Clearance: Appeared to increase with increasing post-menstrual age; strongly associated with SCr and postmenstrual age [4]
Half-life: Decreased with increasing post-menstrual age [4]

Pharmacokinetic Parameters					
Parameters	GA: less than 32 weeks and PNA: less than 2 weeks (20 mg/kg every 12 hours)	GA: less than 32 weeks and PNA: 2 weeks or older (20 mg/kg every 8 hours)	GA: 32 weeks or older and PNA: less than 2 weeks (20 mg/kg every 8 hours)	GA: 32 weeks or older and PNA: 2 weeks or older (30 mg/kg every 8 hours)	Overall
CL (L/hr/kg)	0.089	0.122	0.135	0.202	0.119
V (L/kg)	0.489	0.467	0.463	0.451	0.468
AUC (mcg-hr/mL)	448	491	445	444	467
Cmax (mcg/mL)	44.3	46.5	44.9	61	46.9
Cmin (mcg/mL)	5.36	6.65	4.84	2.1	5.65
T1/2 (hr)	3.82	2.68	2.33	1.58	2.68

Values were obtained from a population pharmacokinetic analysis of sparse data
GA: gestational age; PNA: postnatal age
Merrem IV product information, 2014; AUC is from 0 to 24

ABOUT

Special Considerations/Preparation

Availability: Powder for injection in 500-mg, and 1000-mg vials.
Dilution and Stability
IV Bolus: 10 mL of compatible diluent (500-mg vial) or 20 mL (1000-mg vial) for IV bolus. When reconstituted with sterile water for injection up to 50 mg/mL, stable for up to 3 hours at room temperature or up to 13 hours when refrigerated (at or up to 5 degrees C) [7].
IV Infusion: Concentrations from 1 to 20 mg/mL, in NS, are stable for 1 hour at or up to 25 degrees C or 15 hours at or up to 5 degrees C. Concentrations from 1 to 20 mg/mL, in D_5W, should be used immediately [7].
Some studies demonstrated longer stability times [12][13][14]

Methadone

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Neonatal Abstinence Syndrome
Initial dose: 0.05 to 0.1 mg/kg per dose orally every 6 to 24 hours [1][2][3][4][5]. Adjust dose (in 10% to 20% increments) and weaning schedule based on signs and symptoms of withdrawal [2][4].
Weaning Protocol[6]
Gestational age, 34 weeks or more
Start at step 1 for infants with 3 consecutive Finnegan scores 8 or more or 2 consecutive Finnegan scores 12 or more:

- Step 1: 0.1 mg/kg orally every 6 hours for 4 doses
- Step 2: 0.07 mg/kg orally every 12 hours for 2 doses
- Step 3: 0.05 mg/kg orally every 12 hours for 2 doses
- Step 4: 0.04 mg/kg orally every 12 hours for 2 doses
- Step 5: 0.03 mg/kg orally every 12 hours for 2 doses
- Step 6: 0.02 mg/kg orally every 12 hours for 2 doses
- Step 7: 0.01 mg/kg orally every 12 hours for 2 doses
- Step 8: 0.01 mg/kg orally every 24 hours for 1 dose

Weaning

- Wean to the next step if the average Finnegan score is less than 8 for the past 24 hours
- If the average Finnegan score is 8 to 12, do not wean
- If the average Finnegan score is at least 12, consider an extra dose of methadone at the current step, or return to previous step

Escalation
If the infant fails step 1 (score of greater than 12), consider steps 1A through 1C

- Step 1A: 0.1 mg/kg orally every 4 hours for 6 doses
- Step 1B: 0.1 mg/kg orally every 8 hours for 3 doses
- Step 1C: 0.1 mg/kg orally every 12 hours for 2 doses

Adjunct:
Consider adding phenobarbital if unable to wean for 2 consecutive days
Discharge
Observe for 72 hours from the last dose of step 8

Dose Adjustments
Liver Impairment: Consider lower initial dose and titrate slowly [7][8][9].
Renal Impairment: Consider lower initial dose with longer dosing interval and titrate slowly [7][8][9]
Concomitant benzodiazepines or other CNS depressants: If concomitant use if necessary, limit dosages and durations to the minimum required and consider prescribing naloxone for the emergency treatment of opioid overdose [10].
Concomitant skeletal muscle relaxants: If concomitant use is necessary, consider prescribing naloxone for the emergency treatment of opioid overdose [10].

Uses

Neonatal abstinence syndrome (NAS)[1][2].
Sublingual buprenorphine was associated with the largest reduction in length of treatment and length of stay for NAS in a network meta-analysis of 18 randomized controlled trials (n=1072) of buprenorphine, clonidine, diluted tincture of opium and clonidine, diluted tincture of opium, morphine, methadone, and phenobarbital. Morphine was the least effective opioid [11]. The findings should be interpreted with caution due to significant study limitations [11][12]
Compared with morphine: Methadone outperformed morphine for the treatment of NAS in a multicenter, randomized, double-blind study of 116 term infants (median LOS (16 vs 20 days, p=0.005), LOS attributable to NAS (16 vs 19 days, p=0.005), and length of drug treatment (11.5 vs 15 days, p=0.009)). Initial oral doses were 0.3 mg/kg/day for Finnegan score (FS) of 8 to 10, 0.5 mg/kg/day for FS of 11 to 13, 0.7 mg/kg/day for FS 14 to 16, and 0.9 mg/kg/day for FS of 17 or more. The total daily doses were divided every 4 hours for morphine and every 8 hours for methadone. A nonalcoholic solution of methadone was compounded [13].
Neonatal abstinence syndrome was treated for a median of 14 days with methadone compared with 21 days for morphine (p=0.008) in a double-blind, randomized trial (n=78). All neonates were 35 weeks gestational or more and prenatal exposure was either methadone or buprenorphine [14].
Compared with buprenorphine: A shorter duration of opioid treatment (9.4 vs 14 days) and shorter length of inpatient stay (16.3 vs 20.7 days) with a sublingual buprenorphine protocol compared with oral methadone protocol was demonstrated in a retrospective analysis of 201 infants (34 weeks' gestation or older) with NAS. Infants exposed in utero to methadone were excluded [15].

MEDICATION SAFETY

Contraindications/Precautions

Contraindications
•Significant respiratory depression, in the absence of resuscitative equipment or in unmonitored settings [20][8][9]

•Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment [20][8][9]
•Known or suspected paralytic ileus [20][8][9]
•Known or suspected gastrointestinal obstruction [20][8][9]

Precautions
Administration: Crushing, chewing, or dissolving may result in uncontrolled delivery and increased risk of overdose or death [21].
Administration: The manufacturer suggests that methadone **not** be used as an as-needed (prn) analgesic [21].
Cardiovascular: Severe hypotension, orthostatic hypotension, and syncope have been reported [20][9][8][22]; increased risk in those with reduced blood volume or who use CNS depressants concomitantly; monitoring recommended [20]
Cardiovascular: Avoid use in patients with circulatory shock [20].
Concomitant use: Avoid concomitant use with mixed agonist/antagonist or partial agonists [21][9][8].
Concomitant use: Reserve concomitant prescribing with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol) for patients in whom alternative treatment options are inadequate; profound sedation, respiratory depression, coma, and death may occur; monitoring recommended and dose adjustment may be necessary. Consider prescribing naloxone [10].
Endocrine and metabolic: Opioids may rarely lead to adrenal insufficiency due to inadequate amounts of cortisol. If adrenal insufficiency is suspected, perform diagnostic testing, treat with corticosteroids if confirmed, wean patient off of opioid if appropriate, and continue to assess adrenal function [23].
Endocrine and metabolic: Preexisting hypothyroidism increases the risk for respiratory depression; reduce the initial dose in these patients [24]
Gastrointestinal: Avoid use in patients with gastrointestinal obstruction [9][8].
Hepatic: Spasm of sphincter of Oddi, and worsen biliary tract disease, including acute pancreatitis may occur; monitoring recommended [20][9][8]
Hepatic: Hepatic disease may increase risk of toxicity and CNS depressant effects; use lower initial dose and titrate slowly; monitoring recommended [9][8]
Neurologic: Potentially life-threatening serotonin syndrome has been reported; the risk is increased with concomitant use of serotonergic drugs [23].
Neurologic: Seizure disorders may be induced or aggravated; monitoring recommended [21][9][8]
Neurologic: Severe sedation, coma, and death have been reported [9][8].
Neurologic: Avoid use in patients with impaired consciousness or coma [21].
Neurologic: Use in patients at risk or who have increased intracranial pressure (eg, brain tumors, head injury, intracranial lesions) may exaggerate respiratory depression and sedation and further increase intracranial pressure; opioids may obscure clinical course of head injury; monitoring recommended [21][9][8]
Opioid overdose: Consider prescribing naloxone for the emergency treatment of opioid overdose based on the patient's risk factors for overdose (eg, concomitant use of CNS depressants, history of opioid use disorder, or prior opioid overdose) and if the patient has household members (including children) or other close contacts at risk for accidental exposure or overdose [10].
Prolonged use: Long-term use of opioids may be associated with decreased sex hormone levels and symptoms such as reduced interest in sex, impotence, or infertility. Laboratory

evaluation may be warranted [23].
Renal: Renal disease may increase risk of CNS depressant effects; use lower initial dose and titrate slowly; monitoring recommended [9][8].
Respiratory: Respiratory depression is more likely to occur in cachectic or debilitated patients; monitoring recommended [21][9][8]; reduced initial dose recommended [9][8] and consider prescribing naloxone [10].
Respiratory: Use in patients with preexisting chronic pulmonary disease (eg, COPD, cor pulmonale, asthma) may further decrease respiratory drive leading to apnea, even at therapeutic doses; monitoring recommended and consider nonopioid alternatives if feasible [21][9][8].
Respiratory: Increased risk of decreased respiratory drive, including apnea, in patients with a decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory; monitoring recommended, especially during initiation, dose increases, and concomitant use with other drugs associated with respiratory depression. Alternative therapy may be required [20].
Respiratory: Sleep-related breathing disorders including central sleep apnea and sleep-related hypoxemia may occur and risk increases in a dose-dependent fashion; dose reduction may be necessary [25].
Respiratory: Peak respiratory depressant effect occurs later and persists longer than analgesic effect, which may result in overdose [9][8].
Withdrawal: Severe withdrawal symptoms may occur with abrupt discontinuation [21][9][8] or if a mixed agonist/antagonist or partial opioid agonist is administered with or after full opioid agonist therapy [21].

Adverse Effects

Common side effects of opioids in children include constipation, nausea, vomiting, itching, and urinary retention. There may be unpredictable and limited cross tolerance when switching between other opioids; use caution with dosage conversions [26][27][28][24].

Cardiovascular

QT_C prolongation (450 milliseconds or greater) occurred in 45 out of 89 (50.6%) hospitalized pediatric patients while on methadone in a retrospective study. QT_C prolongation 500 milliseconds or greater) occurred in 18 (20.2%) patients. No events of torsades de pointes occurred. The majority of patients were 1 to 11 months of age (40.4%) and 12 to 35 months (20.2%) and the minority were infants younger than 1 month (6.7%). The median maximum dose was 0.59 mg/kg/day [29].
In a single case report, QTc prolongation was noted in a term infant born to a mother receiving methadone maintenance therapy (50 mg/day). After birth, the infant's resting HR was 80 to 90 beats per minute and ECG showed a QTc of 510 msec. This resolved spontaneously over 5 days [17].

Respiratory Effects

Respiratory depression can occur at excessive doses [16].

Black Box Warning

Warning: Addiction, Abuse And Misuse; Life-Threatening Respiratory Depression; Accidental Ingestion; Life-Threatening QT Prolongation; Neonatal Opioid Withdrawal Syndrome; Interactions With Drugs Affecting Cytochrome P450 Isoenzymes; Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants; And Treatment For Opioid Addiction [19]

- Addiction, Abuse, and Misuse
- Methadone hydrochloride tablets expose patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing methadone hydrochloride tablets, and monitor all patients regularly for the development of these behaviors and conditions
- Life-Threatening Respiratory Depression
- Serious, life-threatening, or fatal respiratory depression may occur with use of methadone hydrochloride tablets. The peak respiratory depressant effect of methadone occurs later, and persists longer than the peak analgesic effect, especially during the initial dosing period or following a dose increase. Monitor for respiratory depression, especially during initiation of methadone hydrochloride tablets or following a dose increase
- Accidental Ingestion
- Accidental ingestion of even one dose of methadone hydrochloride tablets, especially by children, can result in a fatal overdose of methadone
- Life-Threatening QT Prolongation
- QT interval prolongation and serious arrhythmia (torsades de pointes) have occurred during treatment with methadone. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. Closely monitor patients with risk factors for development of prolonged QT interval, a history of cardiac conduction abnormalities, and those taking medications affecting cardiac conduction for changes in cardiac rhythm during initiation and titration of methadone hydrochloride tablets
- Neonatal Opioid Withdrawal Syndrome
- Neonatal opioid withdrawal syndrome (NOWS) is an expected and treatable outcome of use of methadone hydrochloride tablets during pregnancy. NOWS may be life-threatening if not recognized and treated in the neonate. The balance between the risks of NOWS and the benefits of maternal methadone hydrochloride use may differ based on the risks associated with the mother's underlying condition, pain, or addiction. Advise the patient of the risk of NOWS so that appropriate planning for management of the neonate can occur.
- Cytochrome P450 Interaction
- The concomitant use of methadone hydrochloride tablets with all cytochrome P450 3A4, 2B6, 2C19, 2C9 or 2D6 inhibitors may result in an increase in methadone plasma concentrations, which could cause potentially fatal respiratory depression. In addition, discontinuation of concomitantly used cytochrome P450 3A4, 2B6, 2C19, or 2C9 inducers may also result in an increase in methadone plasma concentration. Follow patients closely for respiratory depression and sedation, and consider dosage reduction with any changes of concomitant medications that can result in an increase in methadone levels
- Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants
- Concomitant use of opioids with benzodiazepines or other central nervous system (CNS)

depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

- Reserve concomitant prescribing of methadone benzodiazepines or other CNS depressants for use in patients in methadone treatment for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required
- Follow patients for signs and symptoms of respiratory depression and sedation. If the patient is visibly sedated, evaluate the cause of sedation, and consider delaying or omitting the daily methadone dose
- Conditions For Distribution And Use Of Methadone Products For The Treatment Of Opioid Addiction
- For detoxification and maintenance of opioid dependence, methadone should be administered in accordance with the treatment standards cited in 42 CFR Section 8, including limitations on unsupervised administration

Solution Compatibility

NS.

Terminal Injection Site Compatibility

Atropine sulfate, dexamethasone, lorazepam, metoclopramide, midazolam, and phenobarbital.

Terminal Injection Site Incompatibility

Phenytoin.

Monitoring

Monitor respiratory, central nervous system, and cardiac status closely, especially during drug initiation and titration [7][8][9]. A 12-lead ECG should be obtained on methadone-exposed infants experiencing bradycardia or tachycardia [16][17]. Assess for gastric residuals, abdominal distention, and loss of bowel sounds. For infants experiencing neonatal abstinence syndrome, monitor and score signs of drug withdrawal using a published abstinence assessment tool such as the modified Neonatal Abstinence Scoring System (Finnegan) or the Lipsitz tool [1][18].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Long-acting narcotic analgesic. Oral bioavailability is 50%, with peak plasma levels obtained in 2 to 4 hours. Metabolized extensively via hepatic N-demethylation. Highly protein bound (90% adults). Serum half-life ranges from 16 to 25 hours in neonates and is prolonged in patients with renal failure. Rifampin and phenytoin accelerate the metabolism of methadone and can precipitate withdrawal symptoms.

Factors to consider which differentiate methadone from other opioids [7][8][9]:

- High inter-patient variability in absorption, metabolism, and relative analgesic potency
- Duration of analgesic effect shorter (based on single-dose studies) than the plasma half-life
- Steady-state plasma concentrations, and full analgesic effects, not attained until 3 or more days after initiation of dosing
- Peak respiratory depressant effect occurs later and persists longer than peak analgesic effect
- With repeated dosing, methadone is retained in the liver and slowly released, which prolongs the duration of potential toxicity
- Narrow therapeutic index, especially in combination with other drugs
- High opioid tolerance does not eliminate the possibility of overdose with methadone

ABOUT

Special Considerations/Preparation

Available as oral solutions in 1- and 2-mg/mL concentrations containing 8% alcohol, and a 10-mg/mL alcohol-free solution[8][9] Also available as 5- and 10-mg tablets [7].

Metoclopramide

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Tablets are not recommended for use in pediatric patients due to an increased risk of tardive dyskinesia and other extrapyramidal symptoms, as well as a risk of methemoglobinemia in neonates[1].

0.033 to 0.1 mg/kg/dose orally or IV every 8 hours.

Uses

To **facilitate gastric emptying and gastrointestinal motility**. May improve feeding intolerance. Use in **gastroesophageal reflux** patients is controversial.
(Also used to enhance lactation--10 mg every 8 hours.)
Apnea of prematurity: Reducing gastric acidity or increasing gastric motility for the sole purpose to reduce apnea episodes is not supported by the literature [3].

Administration

Intermittent IV infusion: Dilute to 0.2 mg/mL in D_5W or NS and infuse over a minimum of 15 minutes [2].

MEDICATION SAFETY

Contraindications/Precautions

CONTRAINDICATIONS[1][4]

- In patients when stimulation of gastrointestinal motility may be harmful (eg, presence of gastrointestinal hemorrhage, mechanical obstruction, or perforation)
- In patients with pheochromocytoma (may cause a hypertensive crisis) r other catecholamine-releasing paragangliomas
- In patients with epilepsy
- In patients receiving other drugs that are likely to cause extrapyramidal reactions

- In patients with a history of tardive dyskinesia or a dystonic reaction to metoclopramide (oral)

PRECAUTIONS
Cardiovascular: Catecholamine release and elevated blood pressure may occur [4]; avoid use in patients with hypertension or those taking monoamine oxidase inhibitors [1].
Cardiovascular: Fluid retention and volume overload may occur, especially in patients with cirrhosis or congestive heart failure [4]; discontinue if such reactions occur [1].
Endocrine and metabolic: Hyperprolactinemia may occur and lead to galactorrhea, amenorrhea, or gynecomastia [1].
Neurologic: Neuroleptic malignant syndrome (NMS) has been reported rarely; immediately discontinue use if occurs [4]; avoid use in patients receiving other drugs associated with NMS, such as typical and atypical antipsychotics [1].
Neurologic: Acute dystonic reactions, which may present as stridor and dyspnea, have been reported and usually occur during first 24 to 48 hours of therapy; risk is increased pediatric patients and with higher doses used for prophylaxis of chemotherapy-related vomiting. Treatment of symptoms with diphenhydramine or benztropine may be required [4]; avoid use in patients receiving other drugs likely to cause extrapyramidal symptoms [1].
Neurologic: Tardive dyskinesia (TD), which may be irreversible, may occur; risk increased with duration of treatment and total cumulative dose; discontinue use if signs or symptoms develop [4]; avoid use in patients receiving other drugs likely to cause TD [1].
Neurologic: Parkinsonian-like symptoms (bradykinesia, tremor, cogwheel rigidity, mask-like facies) have been reported within first 6 months of use; symptoms generally resolve following discontinuation [4]; avoid use in patients with Parkinson disease and those being treated with antiparkinsonian drugs [1].
Neurologic: Akathisia (anxiety, agitation, jitteriness, insomnia, pacing, foot tapping) has occurred; if symptoms resolve, consider reinitiating at a lower dosage [1].
Psychiatric: Depression has been reported in patients with and without a history of depression; symptoms may range from mild to severe and include suicidal ideation and suicide [4]; avoid use in patients with a history of depression [1].
Psychiatric: Anxiety and restlessness, followed by drowsiness, may occur with too rapid administration [4].
Surgery: Additional pressure on suture lines following a gut anastomosis or closure may occur due to promotility activity [4].

Adverse Effects

Intended for short-term use (several weeks). Dystonic reactions and extrapyramidal symptoms are seen frequently at higher doses and with prolonged use; children are more susceptible than adults.

Black Box Warning

Tardive Dyskinesia

Treatment with metoclopramide can cause tardive dyskinesia, a serious movement disorder that is often irreversible. The risk of developing tardive dyskinesia increases with duration of treatment and total cumulative dose. Metoclopramide therapy should be discontinued in patients who develop signs or symptoms of tardive dyskinesia. There is no known treatment for tardive dyskinesia. In some patients, symptoms may lessen or resolve after metoclopramide treatment is stopped. Treatment with metoclopramide for longer than 12 weeks should be avoided in all but rare cases where therapeutic benefit is thought to outweigh the risk of developing tardive dyskinesia [1][4].

Solution Compatibility

D_5W and NS.

Terminal Injection Site Compatibility

Acyclovir, aminophylline, atropine, aztreonam, caffeine citrate, cimetidine, ciprofloxacin, clindamycin, dexamethasone, famotidine, fentanyl, fluconazole, heparin, hydrocortisone, lidocaine, linezolid, meropenem, methadone, midazolam, morphine, multivitamins, piperacillin/tazobactam, potassium chloride, potassium phosphate, prostaglandin E_1, quinupristin-dalfopristin, ranitidine, remifentanil, and zidovudine.

Terminal Injection Site Incompatibility

Ampicillin, calcium gluconate, cefepime, chloramphenicol, erythromycin lactobionate, furosemide, penicillin G, propofol, and sodium bicarbonate.

Monitoring

Measure gastric residuals. Observe for increased irritability or vomiting.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Derivative of procainamide. Exact mode of action is unknown; however, metoclopramide has both dopamine-receptor blocking activity and peripheral cholinergic effects. Well absorbed from gastrointestinal tract. Variable first-pass metabolism by liver. Significant fraction

excreted unchanged in urine. Lipid-soluble, large volume of distribution. Serum half-life in adults is 4 hours; prolonged in patients with renal failure.

ABOUT

Special Considerations/Preparation

Available as a 5-mg/mL injectable solution (osmolarity 280 mOsm/kg). **Protect from light.** A dilution made with preservative-free NS is stable for 24 hours at room temperature under normal light or for 48 hours if protected from light [2]. A 0.1 mg/mL dilution may be made by adding 0.4 mL of the 5-mg/mL concentration to 19.6 mL of preservative-free NS.

Oral preparation available in 1-mg/mL concentration. A 0.1 mg/mL oral dilution may be made by adding 1 mL of the 1-mg/mL concentration to 9 mL simple syrup. Stable for 4 weeks at room temperature.

DOSING/ADMINISTRATION

Dose

Anaerobic Infections

Postmenstrual Age	Loading Dose † ‡ ¶ IV or Oral ♦	Maintenance Dose IV or Oral ♦	Interval
24 to 25 weeks	15 mg/kg	7.5 mg/kg † ¶	24 hours † ¶
26 to 27 weeks	15 mg/kg	10 mg/kg † ¶	24 hours † ¶
28 to 33 weeks	15 mg/kg	7.5 mg/kg † ‡	12 hours † ‡
34 to 40 weeks	15 mg/kg	7.5 mg/kg † ‡	8 hours † ‡
Greater than 40 weeks	15 mg/kg	7.5 mg/kg † ‡	6 hours † ‡
Postmenstrual Age = gestational age plus postnatal age ♦ Doses for IV and oral routes are the same in adults for the treatment of anaerobic infections (Product Information metronidazole IV injection, Baxter Healthcare 2011)			
† Dannelley, 2017 ‡ Cohen-Wolkowiez, 2013; Cohen-Wolkowiez, 2012 ¶ Suyagh, 2011			

• Safety and efficacy have not been established with the above regimens [1].
• Dose simulations of the above regimens predict steady-state trough concentrations of greater than 8 mg/L in infants with a gestational age (GA) of 28 weeks or more [2][3] and steady-state concentrations of greater than 6 mg/L throughout the dose interval in infants with GA of 24 to 27 weeks [4].

Surgical Prophylaxis

Less than 1.2 kg: Single 7.5 mg/kg IV dose 60 minutes before surgical incision. Re-dose if the procedure exceeds 2 half-lives of metroNIDAZOLE or there is excessive blood loss during the procedure. If continued postoperatively, the duration should be less than 24 hours, regardless of the presence of intravascular catheters or indwelling drains [5].
1.2 kg or more: Single 15 mg/kg IV dose 60 minutes before surgical incision. Re-dose if the procedure exceeds 2 half-lives of metroNIDAZOLE or there is excessive blood loss during the procedure. If continued postoperatively, the duration should be less than 24 hours,

regardless of the presence of intravascular catheters or indwelling drains [5].

Dosage Adjustment
Severe Hepatic Impairment (Child-Pugh C): Reduce dose by 50% [6][7].

Uses

Anaerobic Infections: Metronidazole is effective for anaerobic infections and protozoal parasites but it is not approved in infants [6][7]. Common uses in premature infants are for the treatment of anaerobic bacteremia and central nervous system infections [9].

*Clostridium difficile***infection:** Young children and infants may be asymptomatically colonized, but are unlikely to be infected with *C difficile*. Routine testing for *C difficile* in neonates or infants 12 months or younger with diarrhea is not recommended [10] .

Clinical Definition	Recommendation
Initial episode, non-severe	MetroNIDAZOLE or Vancomycin
Initial episode, severe/fulminant	Vancomycin +/- IV metroNIDAZOLE (when critical illness is present)
First recurrence, non-severe	MetroNIDAZOLE or Vancomycin
Second or subsequent recurrence	Vancomycin •For 10 days followed by rifAXIMin* for 20 days OR •As a tapered and pulsed regimen OR Fecal microbiota transplantation (after multiple recurrences)
McDonald, 2017	
* Pediatric dosing not available for rifAXIMin; no FDA approved uses for patients younger than 12 years.	

Necrotizing enterocolitis: The recommended IV broad-spectrum antibiotics are a combination of ampicillin, gentamicin, and metroNIDAZOLE; ampicillin, cefotaxime, and metroNIDAZOLE; or meropenem. Vancomycin is an alternative to ampicillin when MRSA or ampicillin-resistant enterococcal infection is suspected [11].

Administration

Intravenous:
•Infuse over 30 to 60 minutes at a final concentration not to exceed 8 mg/mL (administer by slow IV drip infusion only, either as a continuous or intermittent infusion) [8].
•Do NOT use equipment containing aluminum (eg, needles, cannulae) that would come in contact with the drug solution [8].
•Do not introduce additives into injection; if used with a primary IV fluid system, discontinue the primary solution during infusion [8].

MEDICATION SAFETY

Contraindications/Precautions

Contraindications[18][19][20][21]

- Alcohol (or products containing propylene glycol) use during and for at least 3 days after metroNIDAZOLE use (oral, Flagyl(R) IV)
- Concomitant use with or within the last 2 weeks of disulfiram (oral, Flagyl(R) IV)
- Hypersensitivity to metroNIDAZOLE or any other component of the product or to other nitroimidazole agents
- Cockayne syndrome (oral, IV)

Precautions
Endocrine and metabolic: Sodium retention may occur due to sodium content of injectable formulation; caution in patients receiving a controlled sodium diet, corticosteroids, or patients who are predisposed to edema [18].
Hematologic: Agranulocytosis, neutropenia, and leukopenia has been reported [18]; increased risk in patients with current or history of blood dyscrasias [18][19]; monitoring recommended [22][18][19].
Hepatic: Decreased metronidazole metabolism may occur in patients with hepatic impairment; monitoring recommended and dose adjustment may be required [18][19].
Hepatic: Decreased metronidazole metabolism may occur in patients with severe hepatic encephalopathy; dose adjustment may be required [18].
Immunologic: Candidiasis superinfection has been reported and may present more prominent symptoms during therapy [22][18][19][20].
Laboratory abnormalities: Laboratory test interference may occur with some serum chemistry values (eg, AST, ALT, LDH, triglycerides, glucose hexokinase); consider postponing laboratory tests until treatment complete (vaginal gel) [23].
Neurologic: Severe neurological disturbances, including encephalopathy associated with cerebellar toxicity (characterized by ataxia, dizziness, dysarthria, nystagmus [18][19][20][23] and saccadic pursuit [18]), convulsive seizures, peripheral neuropathy, and aseptic meningitis has been reported; discontinuation may be required [22][18][19][20][23].
Neurologic: Abnormal neurologic signs and symptoms have been reported; evaluation of the benefit/risk ratio of continuation of therapy may be necessary [22][19][20].
Ophthalmic: Optic neuropathy has been reported [18][19].
Renal: Reduced urinary metronidazole excretion has been reported in patients with severe renal impairment and ESRD not undergoing hemodialysis [18][19][19] and with peritoneal

dialysis [18]; monitoring recommended [18][19][19].

Adverse Effects

The most common adverse reactions are related to the gastrointestinal tract, particularly nausea, sometimes accompanied by headache, anorexia, and occasionally vomiting, diarrhea, epigastric distress, abdominal cramping, and constipation [8]

Black Box Warning

MetroNIDAZOLE has been shown to be carcinogenic in mice and rats. Unnecessary use of the drug should be avoided. Its use should be reserved for the conditions described in the Indications and Usage section of the package insert [6].

Solution Compatibility

D_5W, and NS.

Solution Incompatibility

Manufacturer recommends that if metroNIDAZOLE is used with a primary IV fluid system, the primary solution should be discontinued during metroNIDAZOLE infusion.

Terminal Injection Site Compatibility

Acyclovir, amikacin, amiodarone, ampicillin, caspofungin, cefazolin, cefepime, cefotaxime, cefoxitin, ceftazidime, ceftriaxone, chloramphenicol, clindamycin, dopamine, enalaprilat, esmolol, fluconazole, gentamicin, heparin, hydrocortisone succinate, linezolid, lorazepam, magnesium sulfate, midazolam, milrinone, morphine, netilmicin, nicardipine, penicillin G, piperacillin-tazobactam, prostaglandin E_1, remifentanil, and tobramycin.

Terminal Injection Site Incompatibility

Aztreonam and meropenem.

Monitoring

•Consider culture and susceptibility information before treatment initiation and with therapy modifications whenever possible [8][12][13][14].
•Confirm trichomonad infection with wet smears, cultures, or both before treatment initiation. Repeat cultures or smears after treatment cessation to confirm eradication and before repeated treatment [12][14].
•Perform total and differential leukocyte counts both before and after therapy [12][14][13] and in patients who require prolonged or repeated treatment [8].
•Monitor patients with ESRD or hepatic impairment for drug-associated adverse events [12][14].
•In patients with Cockayne syndrome, obtain a liver function test prior to therapy initiation, within the first 2 to 3 days after initiation, frequently during therapy, and after discontinuing therapy [15][16][17].
•Observe patients with Cockayne syndrome for signs and symptoms for potential liver injury (eg, abdominal pain, nausea, change in stool color, or jaundice) [16][15][17].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action: MetroNIDAZOLE is a nitroimidazole antibiotic and is bactericidal for many anaerobic organisms (bacteria and protozoa). The drug exhibits concentration-dependent bactericidal activity with a post-antibiotic effect of greater than 3 hours [24]. Metronidazole exerts antibacterial effects in an anaerobic environment against most obligate anaerobes. Once metronidazole enters the organism by passive diffusion and activated in the cytoplasm of susceptible anaerobic bacteria, it is reduced; this process includes intracellular electron transport proteins such as ferredoxin, transfer of an electron to the nitro group of the metronidazole, and formation of a short-lived nitroso free radical. Because of this alteration of the metronidazole molecule, a concentration gradient is created and maintained which promotes the drug's intracellular transport. The reduced form of metronidazole and free radicals can interact with DNA leading to inhibition of DNA synthesis and DNA degradation leading to death of the bacteria. The precise mechanism of action of metronidazole is unclear [22]..

Pharmacokinetics
Absorption: Oral metroNIDAZOLE is well absorbed [6].
Distribution
Volume of distribution: Median Vd was 0.71 L/kg for 32 infants with a median gestational age of 27 weeks (median postnatal age of 41 (0 to 97) days; postmenstrual age 32 (24 to 43) weeks; and weight 1,4954 (678 to 3,850) g). [3].
Concentration is CSF is similar to concentration in plasma [6].
Protein-binding: less than 20% protein bound [6].
Metabolism: Newborns have diminished capacity to eliminate metroNIDAZOLE [6]

Clearance: Median clearance parameters for 32 infants were: [3].

- 0.024 L/hrs/kg; gestational age of less than 26 (median postnatal age, 53 days (7 to 97 days))
- 0.026 L/hrs/kg; gestational age 26 to 29 weeks (median postnatal age, 32 days (0 to 97 days))
- 0.029 L/hrs/kg; gestational age 30 to 32 weeks (median postnatal age, 33 days (8 to 71 days))

Half-life:
Newborn infants: When measured during the first 3 days of life, was inversely related to gestational age [22].
Gestational ages between 28 and 40 weeks: Ranged from 109 to 22.5 hours [22].
Median half-lives for 32 infants were: [3].

- 20.5 hours; gestational age of less than 26 (median postnatal age, 53 days (7 to 97 days))
- 18.6 hours; gestational age 26 to 29 weeks (median postnatal age, 32 days (0 to 97 days))
- 16.7 hours; gestational age 30 to 32 weeks (median postnatal age, 33 days (8 to 71 days))

ABOUT

Special Considerations/Preparation

Injection
Availability: 5 mg/mL in 100 mL single-dose plastic ready-to-use solution containers and 500-mg vials.
Storage: For the ready-to-use solution, protect from light **until use and store at controlled room temperature. Do not refrigerate (crystals form, but redissolve on warming to room temperature). For the vial store below 77 degrees F and protect from light.**
Reconstitution of Vial: Add 4.4 mL of bacteriostatic water for injection, 0.9% sodium chloride, or bacteriostatic 0.9% sodium chloride for a final concentration of approximately 100 mg/mL. The pH is 0.5 to 2. Solution must be further diluted and neutralized. Reconstituted vials are stable for 96 hours when stored below 86 degrees F in room light [8].
Dilution and Neutralization (vial product)
Dilution: Add to glass or plastic IV container not to exceed 8 mg/mL. May use 0.9%, D_5W, or lactated ringer's injection [8].
Neutralization: Neutralize the solution with 5 mEq of sodium bicarbonate injection for each 500 mg of metroNIDAZOLE used. Mix thoroughly. The resultant pH should be 6 to 7. Relieve any gas pressure due to the generation of carbon dioxide accumulation from the neutralization pressure. Do not refrigerate neutralized solution; precipitation may occur . Use within 24 hours of mixing [8].

Oral
Availability: 250-mg and 500-mg tablets for oral administration; 50 mg/mL oral suspension.
Storage (oral suspension): Store at a controlled room temperature between 20 and 25 degrees C (68 to 77 degrees F). Brief exposure between 15 and 30 degrees C (59 and 86 degrees F) permitted. Dispense in a tight container as defined in USP; discard 10 days after opening container Do not freeze [22].

Extemporaneous Oral Suspension
Oral suspension 15 mg/mL may be prepared by crushing thirty (30) metroNIDAZOLE 250-mg tablets (7500 mg), dissolving powder in 10 mL Water for Irrigation, then adding chocolate-cherry syrup* to make a total volume of 500 mL. Shake well. Suspension is stable for 60 days refrigerated.
***Chocolate-cherry syrup: Add 0.6 mL artificial wild cherry flavor to 300 mL simple syrup BP, mix well. Then add chocolate syrup (Nestle Quik®) to cherry syrup to a total volume of 500 mL, mix well. This suspension was judged most palatable versus a chocolate, wild cherry, or plain suspension [25].**

Oral suspension 50 mg/mL may be prepared by adding 12 mL of the vehicle* to 6 grams metroNIDAZOLE powder (equivalent to twenty-four (24) 250-mg tablets) in a mortar and mix to a uniform paste. Add the vehicle in geometric portions and mix thoroughly after each addition. Transfer the contents of the mortar to the calibrated bottle. Add vehicle to the total volume of 120 mL. Protect from light. Shake well. Suspension is stable for 60 days refrigerated or at room temperature (5 and 25 degrees C).

***Vehicles: 1:1 mixture of Ora-Sweet® and Oral-Plus®; 1:1 mixture of Ora-Sweet® SF and Oral-Plus®; or cherry syrup (cherry syrup concentrate diluted 1:4 with simple syrup) [26].**

Micafungin

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Acute Disseminated Candidiasis
Without meningoencephalitis and/or ocular dissemination: 4 mg/kg IV once daily [1].

Candida **Peritonitis and Abscess**
Without meningoencephalitis and/or ocular dissemination: 4 mg/kg IV once daily [1].

Candidemia
Without meningoencephalitis and/or ocular dissemination: 4 mg/kg IV once daily [1].
Duration of therapy for candidemia, without metastatic complications, is 2 weeks after documented clearance of *Candida* from the bloodstream and resolution of symptoms [2].

Candidiasis - HIV Infection
Esophageal disease:
• **Neonates (alternate therapy):** Up to 10 to 12 mg/kg IV daily may be required to achieve therapeutic concentrations. Continue treatment for at least 3 weeks and for at least 2 weeks following resolution of symptoms [3]
Invasive disease:
• **Critically-ill, neonates:** Up to 10 to 12 mg/kg IV daily may be required to achieve therapeutic concentrations. Duration of treatment is based on presence of deep-tissue foci and clinical response; in patients with candidemia, treat until 2 weeks after a positive blood culture [3]

Uses

Neonatal Candidiasis, Including CNS Infection[2]
Invasive candidiasis and candidemia, or very low-birth weight infants with asymptomatic candiduria .

- Amphotericin B deoxycholate is recommended.
- Fluconazole IV or oral is an alternative for those who have not been receiving prophylaxis with fluconazole.
- Lipid formulation amphotericin B agent is an alternative; however, use with caution, especially in the presence of urinary tract involvement.
- Echinocandins (caspofungin, anidulafungin, or micafungin) should be limited to salvage therapy or scenarios of resistance or toxicity to amphotericin B deoxycholate or

fluconazole

Central nervous system infections

- Amphotericin B deoxycholate is recommended.
- Liposomal amphotericin B agent is an alternative.
- Salvage therapy with flucytosine may be added in those patients who have not responded to initial therapy.
- Fluconazole may be used as step-down therapy for fluconazole-susceptible isolates in those patients who respond to initial therapy

Neonatal intensive care unit (with greater than 10% rate of invasive candidiasis)

- Prophylaxis with IV or oral fluconazole for 6 weeks is recommended for neonates with birth weights of less than 1000 g
- Prophylaxis with oral nystatin is an alternative in neonates with birth weights of less than 1500 g when fluconazole is unavailable or fluconazole resistance is present

Candidiasis - HIV infection: Micafungin is recommended as a first-line agent to treat invasive candidiasis in critically-ill patients with HIV co-infection [3]
In the United States, optimal dosing for infants younger than 4 months is not yet established. Studies indicate linear PK; age and clearance are inversely related [3]

Comparison to Amphotericin B: There was no difference in clinical response between echinocandins and amphotericin B (OR 1.38; 95% CI, 0.68 to 2.8) for the treatment of suspected or confirmed invasive candidiasis in a meta-analysis (n=5; 354 neonates and children). Antifungals included were micafungin, caspofungin, amphotericin B deoxycholate, and liposomal amphotericin B. Subanalysis demonstrated no difference in other comparisons including mycological response, mortality, recurrence of candida infection, type of echinocandin, different risk groups (high-risk, low-risk, or neutropenic groups), and type of use (targeted or empirical). Discontinuation due to adverse effects were higher with amphotericin B than the echinocandins (OR 0.3; 95% CI, 0.12 to 0.76) [6].

Pediatric FDA Approved Indications
Micafungin is indicted for: [1]

- Acute disseminated candidiasis without meningoencephalitis and/or ocular dissemination in pediatric patients younger than 4 months
- Candida peritonitis or abscesses without meningoencephalitis and/or ocular dissemination in pediatric patients younger than 4 months
- Candidemia in pediatric patients younger than 4 months without meningoencephalitis and/or ocular dissemination

•The safety and effectiveness of micafungin for the treatment of candidiasis (acute disseminated and candidemia) without meningoencephalitis and/or ocular dissemination in patients younger than 4 months is based on evidence from studies in adult and pediatric patients 4 months or older with additional pharmacokinetic and safety data in pediatric patients younger than 4 months
Limitations:[1]

- Safety and effectiveness of micafungin have not been established for the treatment of

candidemia with meningoencephalitis and/or ocular dissemination in pediatric patients younger than 4 months of age as a higher dose may be needed

- Micafungin has not been adequately studied in patients with endocarditis, osteomyelitis and meningoencephalitis due to Candida
- Efficacy of micafungin against infections caused by fungi other than Candida has not been established

Administration

Administer by intermittent IV infusion over 1 hour at a concentration between 0.5 to 1.5 mg/mL [4]. The recommended concentration is 1 mg/mL [5]. Existing IV line should be flushed with NS prior to administration. Concentrations higher than 1.5 mg/mL (up to 4 mg/mL) should be administered through a central line [4].

MEDICATION SAFETY

Contraindications/Precautions

Hematologic: Acute intravascular hemolysis and hemolytic anemia have been reported [7].
Hepatic: Hepatic abnormalities (eg, liver function test (LFT) abnormalities, significant hepatic impairment, hepatitis, hepatic failure) have occurred. Evaluate risk vs benefit of continued treatment if abnormal liver function tests develop [7].
Immunologic: Hypersensitivity reactions (eg, anaphylaxis, shock) have been reported. Discontinue use if hypersensitivity occurs and institute appropriate treatment [7]
Immunologic: Infusion reactions have been reported including rash, pruritus, facial swelling, and vasodilatation; slow the infusion rate if reaction occurs [1]
Immunologic: Injection site reactions, including phlebitis and thrombophlebitis, have been reported with doses of 50 to 150 mg/day; occurs more often in patients receiving micafungin via a peripheral IV [1]
Renal: Hemoglobinuria and renal dysfunction (eg, BUN or creatinine elevations, significant renal impairment, acute renal failure) have been reported [7].

Adverse Effects

Most common adverse events (2% to 3%) reported in pediatric clinical trials were hypokalemia, increases in AST, ALT, bilirubin, or alkaline phosphatase levels, abnormal liver function tests, and hypertension. More severe hepatic dysfunction, hepatitis, and hepatic failure have also been reported. Pediatric patients (especially less than 1 year of age) appear to be at higher risk than adults for developing liver injury. Neutropenia, thrombocytopenia,

and hypomagnesemia also occurred in less than 2% of patients. Other common adverse events include nausea, vomiting, diarrhea, and rash [8][9][10].

Solution Compatibility

D_5 W, D_5 1/4 NS, LR, and NS.

Terminal Injection Site Compatibility

Micafungin diluted to 1.5 mg/mL
Aminophylline (2.5 mg/mL), bumetanide (40 mcg/mL), calcium chloride (40 mg/mL), calcium gluconate (40 mg/mL), cyclosporine (5 mg/mL), dopamine (3.2 mg/mL), esmolol 10 mg/mL), furosemide (3 mg/mL), heparin (100 units/mL), hydromorphone (0.5 mg/mL), lidocaine (10 mg/mL), lorazepam (0.5 mg/mL), magnesium sulfate (100 mg/mL), milrinone (0.2 mg/mL), nitroglycerin (0.4 mg/mL), potassium chloride (0.1 mEq/mL), sodium nitroprusside (2 mg/mL), tacrolimus 20 mcg/mL), theophylline (4 mg/mL), vasopressin (1 unit/mL).

Terminal Injection Site Incompatibility

Albumin, amiodarone, diltiazem, dobutamine, epinephrine, insulin, labetalol, levofloxacin, midazolam, morphine, mycophenolate mofetil, nicardipine, octreotide, ondansetron, phenytoin, rocuronium, and vecuronium.

Monitoring

Assess IV site for signs of irritation. Periodic measurement of serum potassium, calcium, BUN, hepatic transaminases, and creatinine (isolated renal dysfunction reported in adults). For candidemia, monitor blood cultures daily or every other day until *Candida* is cleared [2].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of Action: Micafungin is a semisynthetic lipopeptide echinocandin antifungal agent with broad-spectrum fungicidal activity against many *Candida* species. It inhibits the synthesis of 1, 3-beta-D-glucan, an integral component of the fungal cell wall [11].

Pharmacokinetics
Distribution
Protein binding: Greater than 99% [1]
Primary binding protein is albumin; however, micafungin, at therapeutically relevant concentrations, does not competitively displace bilirubin binding to albumin. Micafungin also binds to a lesser extent to α1-acid glycoprotein [1].
Volume of Distribution: Median Vd was 0.354 L/kg (95% CI, 0.225 to 0.482) in 18 neonates a median 12.5 days of age (range, 3 to 115 days; median gestational age 26 weeks + 6 days) [12].
Metabolism: Arylsulfatase is the enzyme responsible for metabolism of micafungin to the M-1 (catechol form) metabolite. Catechol-O-methyltransferase is the enzyme responsible for further metabolism of the M-1 metabolite to the M-2 (methoxy form) metabolite.
Hydroxylation of the side chain, at the omega-1 position, catalyzed by CYP450 isoenzymes, creates the M-5 metabolite; however, hydroxylation by CYP3A is not a major metabolic pathway for micafungin *in vivo*[1].
Micafungin is neither a P-glycoprotein substrate nor inhibitor *in vitro*. Micafungin is weak inhibitor of CYP3A [1].
Excretion: Fecal excretion is the major route of elimination [1].
Clearance: A population pharmacokinetic analysis of pooled data from 47 neonates and young infants (weight range 0.54 to 4.5 kg) revealed a weight-adjusted clearance that was higher than that reported for older infants and adults (0.043 L/hr/kg vs 0.017 L/hr/kg), which would necessitate use of a higher mg/kg/day dosage to achieve comparable systemic AUCs [13].
Median clearance was 0.02 L/hr/kg (95% CI, 0.01 to 0.023) in 18 neonates a median 12.5 days of age (range, 3 to 115 days; median gestational age 26 weeks + 6 days) [12]
Half-life: Median half-life was 13.6 hours (95% CI, 9.9 to 21.7 hours) in 18 neonates a median 12.5 days of age (range, 3 to 115 days; median gestational age 26 weeks + 6 days) [12]

AUC
•.A mean steady-state AUC of 13 1+/- 50 mcg x hr/mL was produced after 4 mg/kg/day IV in pediatric patients 4 months or younger. This AUC was comparable to AUCs achieved in pediatric patients 4 months or older administered 2 mg/kg/day and adults administered 100 mg/day [1].
•A median loading dose of 15.1 mg/kg followed by 9.9 mg/kg/day (95% CI, 8.1 to 11.4 mg/kg/day) IV attained a median $AUC_{0 \text{ to } 24}$ of 493.8 mg x hr/L (95% CI,, 437.5 to 1023.9) at steady state in 18 neonates with suspected or confirmed systemic candidiasis. Neonates postnatal ages were a median 12.5 days (range, 3 to 115 days; median gestational age 26 weeks + 6 days) [12].
•The predicted $AUC_{0 \text{ to } 24 \text{ hours}}$ was 336 mg x hr/L with a 10-mg/kg/day IV dose in 18 neonates (ranges: gestational age 26.9 to 39 weeks, postnatal age 0.107 to 6.07 months) [14].
•In a study of young infants (median age 18 days (range 3 to 119 days); median gestational age 25 weeks (range 24 to 40 weeks); median weight 1210 g (range 540 to 4500 g) receiving 4 or more days of micafungin treatment; the mean area under the concentration-time curve $AUC_{(0 \text{ to } 24 \text{ hours})}$ was 307.6 +/- 173.7 mcg x hour/mL and 308 +/- 100.6 mcg x hour/mL for patients receiving 7 mg/kg/day (body weight 1000 g or greater; n=6) or 10 mg/kg/day (body weight less than 1000 g; n=6), respectively [15].

•In 12 neonates (median birth weight 775 g, gestational age 27 weeks, and 4 days postnatal), 15 mg/kg/day IV for 5 days resulted in a mean $AUC_{0 \text{ to } 24 \text{ hours}}$ of 437.5 mcg x hr/mL, CL of 0.0365 L/hr, and V_{SS} of 1.6 L. A 15-mg/kg/day IV dose in this population was suggested to correlate with 5 mg/kg/day IV in adults [16].
•In a study of 15 premature neonates (mean gestational age, 26.4 +/- 2.4 weeks), weighing more than 1000 grams (mean weight, 1497 +/- 303 grams), who received a single intravenous dose of micafungin 0.75 mg/kg, 1.5 mg/kg or 3 mg/kg infused over 30 minutes, the area under the concentration-time curve (AUC 0 to 24 hours) was 19 +/- 7.3 (10.3-28.3) mcg/hour/mL, 34.5 +/- 5.6 (29.7-42.1) mcg/hour/mL, and 69 +/- 19.2 (48.9-93.1), respectively (heresi, 2006)[17].

•A population pharmacokinetic analysis of serum level data from 47 neonates who received micafungin in 3 clinical trials determined that a dose of 10 mg/kg was required to achieve a targeted MIC/AUC ratio in simulated patients for most strains of *Candida albicans*. For more resistant strains having a higher MIC of 0.125 mg/L, a dose of 12 mg/kg produced the targeted AUC/MIC ratio in approximately 90% of simulated patients [13].

Extracorporeal Membrane Oxygenation (ECMO): The pharmacokinetic parameters were clearance 0.041 L/kg/hr, Vd 0.64 L/kg, and half-life 11 hours for micafungin in infants (median 59 days (0 to 574 days); gestational age 39 weeks (27 to 39 weeks)) supported by ECMO (n=12). The $AUC_{(0 \text{ to } 24 \text{ hours})}$ was 74 mgXhr/L for the 11 infants on 4 mg/kg/day of IV micafungin. The ECMO circuits used were S3 and CardioHelp. Dose simulations predicted $AUC_{(0 \text{ to } 24 \text{ hours})}$ of 37.5 to 69.5 mgXhr/L within 24 hours with 2.5 mg/kg/day infused over 1 hour and 75 to 139 mgXhr/L with 5 mg/kg/day [18].

ABOUT

Special Considerations/Preparation

Available: Single-use lyophilized powder for injection in vials containing 50 and 100 mg. Preservative free.
Reconstitution: Add 5 mL of 0.9% sodium chloride injection (without bacteriostatic agent) or D_5W to each 50 mg or 100 mg vial yielding approximately 10 mg or 20 mg per mL, respectively. Inspect reconstituted vials for particulate matter and discoloration prior to administration. Gently dissolve lyophilized powder by swirling the vial to avoid excessive foaming. Do not shake [4].
Storage: Reconstituted vials may be stored at room temperature for up to 24 hours before use. Protect from light. Discard partially used vials [4].

Dilution: Reconstituted drug should be further diluted in NS or D_5 W to a final concentration between 0.5 to 1.5 mg/mL prior to administration. Diluted infusion should be protected from light and may be stored at room temperature for up to 24 hours before use. An existing IV line should be flushed with NS prior to administration.

Microlipid

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Microlipid is a 50% safflower oil fat emulsion with 4.5 calories/mL. Used to supplement orally, or added to tube feeding formulas. Mixes easily with enteral formulas.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Osmolality (mOsm/kg water): Not available

Supplied: 48 three ounce bottles per case.

Ingredients: Safflower oil, water, polyglycerol esters of fatty acids, soy lecithin, xanthan gum, ascorbic acid.

Microlipid			
Nutrient	**per mL**	**per 15 mL (1 tbsp)**	**per 89 mL (3 fl oz)**
Calories	4.5	67.5	400
Protein, g	0	0	0
Fat, g	0.5	7.5	44
Carbohydrate, g	0	0.04	0
Water, g	0.45	6.7	40
Linoleic Acid, g	0.4	5.9	35

Fatty Acid Distribution	
Polyunsaturated	78%
Monounsaturated	12%
Saturated	10%
PUFA:SFA	8:1

ABOUT

Special Considerations/Preparation

For oral use only. Do not give parenterally (IV). Shake well before opening. Opened product should be recapped, refrigerated, and discarded after 5 days. Store unopened bottles at room temperature. Protect from freezing.

Midazolam

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

KIDs List: Avoid in very low birth weight neonates due to risk of severe intraventricular hemorrhage, periventricular leukomalacia, or death [1]
Sedation:
IV: 0.05 to 0.15 mg/kg. Repeat as required, usually every 2 to 4 hours. May also be given IM. Dosage requirements are decreased by concurrent use of narcotics.

Continuous IV infusion: 0.01 to 0.06 mg/kg per hour (10 to 60 mcg/kg/hour). Dosage may need to be increased after several days of therapy because of development of tolerance and/or increased clearance.

Intranasal: 0.2 to 0.3 mg/kg per dose using 5-mg/mL injectable form.

Sublingual: 0.2 mg/kg per dose using 5-mg/mL injectable form mixed with a small amount of flavored syrup.

Oral: 0.25 mg/kg per dose using Versed® oral syrup.

Anticonvulsant:
Loading dose: 0.15 mg/kg (150 mcg/kg) IV, followed by maintenance dose.
Maintenance infusion: 0.06 to 0.4 mg/kg per hour (1 to 7 mcg/kg per minute).

Uses

Anesthesia induction

Sedative/hypnotic: Efficacy could not be validated and safety concerns were raised in a review of 3 studies (n=146 preterm neonates) of continuous infusion midazolam (30 to 60 mcg/kg/hr) for procedural sedation in the neonatal intensive care unit [5].

Refractory seizures

Administration

Intravenous: Administer slow IV push over 10 minutes at a concentration of 1 to 5 mg/mL [2][3]. The recommended standard neonatal concentration is 1 mg/mL [4]. For continuous IV

infusion, may dilute in NS or D_5W to a concentration of 0.5 mg/mL. Caution should be taken to avoid intra-arterial injection or extravasation [4][2][3].

MEDICATION SAFETY

Contraindications/Precautions

Contraindications
•Allergy to cherries (Oral syrup) [8]
•Acute narrow-angle glaucoma [9][10][2][11]
•Open-angle glaucoma, untreated [9]

Precautions
Cardiovascular: Hypotension is common when used in conjunction with narcotics, or following rapid bolus administration [10][2][11]
Cardiovascular: Serious cardiorespiratory events, including cardiac arrest resulting in death or permanent injury have been reported with use of midazolam [9]
Cardiovascular: Rarely hypotensive episodes requiring treatment during or after diagnostic or surgical manipulations have been reported; increased risk in patients with hemodynamic instability or in those premedicated with a narcotic [9].
Concomitant use: Avoid or minimize concomitant use of CNS depressants and other substances associated with abuse, misuse, and addiction (eg, opioid analgesics, stimulants) [12].
Endocrine or metabolic: Use particular caution in uncompensated acute illness (eg, severe fluid or electrolyte disturbances) [6]
Neurologic: CNS depression may occur; increased risk with concomitant use of alcohol, other CNS depressants (eg, opioids), barbiturates, and moderate or strong CYP3A4 inhibitors [9].
Neurologic: Impaired cognitive function has been reported; caution against operating hazardous machinery or a motor vehicle until drug effects (eg, drowsiness) subsides; in pediatric patients ensure safe ambulation [9].
Neurologic: Partial or complete impairment of recall may exist for several hours following an administered dose [9].
Neurologic: Brain development in children may be affected by repeated or lengthy use of general anesthetic and sedation drugs during surgeries or procedures, especially in children younger than 3 years or in fetuses of pregnant women during the third trimester; balance appropriate anesthesia use and timing of elective procedures that can be delayed against potential risks in children younger than 3 years and pregnant women, particularly with procedures that are longer than 3 hours or multiple procedures [13].
Ophthalmic: May increase intraocular pressure in patients with glaucoma; may be used in patients with open-angle glaucoma only if they are receiving appropriate therapy; monitoring is recommended [9].
Psychiatric: Antiepileptic drugs, including midazolam, may increase the risk of suicidal thoughts or behavior; monitoring is recommended [9].
Psychiatric: Agitation, involuntary movements (including tonic/clonic movements and muscle tremor), hyperactivity, and combativeness have been reported with midazolam when

used for sedation; consider the possibility of cerebral hypoxia or true paradoxical reactions [9].
Respiratory: Serious respiratory events including respiratory depression, airway obstruction, oxygen desaturation, apnea, respiratory arrest, sometimes resulting in death or permanent injury have been reported with use of midazolam; the risk is greatest in those with chronic obstructive pulmonary disease, chronic disease states, or decreased pulmonary reserve, and concomitant use of barbiturates, alcohol, or other CNS depressants [9].
Special populations: Gasping syndrome or other severe or fatal adverse effects can occur in neonates and low birth weight infants, as formulation contains benzyl alcohol [7]
Surgery: Risk of desaturation and hypoventilation from partial airway obstruction increased in pediatric patients undergoing procedures involving upper airway (eg, upper endoscopy, dental care); those with cardiac or respiratory compromise may be unusually sensitive. Dosage adjustment may be required in higher-risk patients [6][14]
Withdrawal: Symptoms of withdrawal have occurred following discontinuation [6][14]
Withdrawal: In some cases, benzodiazepine users have experienced a protracted withdrawal syndrome with symptoms lasting weeks to more than 12 months [12].

Adverse Effects

Respiratory depression and hypotension are common when used in conjunction with narcotics, or following rapid bolus administration. Seizure-like myoclonus has been reported in 8% of premature infants receiving continuous infusions - this also may occur following rapid bolus administration and in patients with underlying CNS disorders. Nasal administration may be uncomfortable because of a burning sensation.

Black Box Warning

Midazolam has been associated with respiratory depression and respiratory arrest, especially when used for sedation in noncritical care settings. Use only in settings that can provide for continuous monitoring of respiratory and cardiac function. The initial dose and all subsequent doses should always be titrated slowly [6]. Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Monitor patients for respiratory depression and sedation [7].

Midazolam hydrochloride should not be administered by rapid injection in the neonatal population. Severe hypotension and seizures have been reported following rapid IV administration, particularly with concomitant use of fentanyl [6].

Solution Compatibility

D_5W, NS, and sterile water for injection.

Terminal Injection Site Compatibility

Amikacin, aminophylline, amiodarone, atropine, calcium gluconate, cefazolin, cefotaxime, cimetidine, clindamycin, digoxin, dobutamine, dopamine, epinephrine, erythromycin lactobionate, esmolol, famotidine, fentanyl, fluconazole, gentamicin, glycopyrrolate, heparin, imipenem/cilastatin, insulin, linezolid, lorazepam, methadone, metoclopramide, metronidazole, milrinone, morphine, nicardipine, nitroglycerin, nitroprusside, pancuronium bromide, piperacillin, potassium chloride, propofol, ranitidine, remifentanil, theophylline, tobramycin, vancomycin, and vecuronium.

Terminal Injection Site Incompatibility

Fat emulsion. Albumin, ampicillin, bumetanide, cefepime, ceftazidime, dexamethasone, fosphenytoin, furosemide, hydrocortisone succinate, micafungin, nafcillin, and sodium bicarbonate.

Monitoring

Follow respiratory status and blood pressure closely, especially when used concurrently with narcotics. Assess hepatic function. Observe for signs of withdrawal after discontinuation of prolonged therapy.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action: Relatively short-acting benzodiazepine with rapid onset of action. Sedative and anticonvulsant properties related to GABA accumulation and occupation of benzodiazepine receptor. Antianxiety properties related to increasing the glycine inhibitory neurotransmitter [10][2].

Metabolized by hepatic CYP3A4 to a less active hydroxylated metabolite, then glucuronidated before excretion in urine. Drug accumulation may occur with repeated doses, prolonged infusion therapy, or concurrent administration of cimetidine, erythromycin or fluconazole. Highly protein bound. Duration of action is 2 to 6 hours.
Elimination half-life is approximately 4 to 6 hours in term neonates, and quite variable, up to 22 hours, in premature babies and those with impaired hepatic function.
Bioavailability is approximately 36% with oral administration and 50% with sublingual and intranasal administration.
Midazolam is water soluble in acidic solutions and becomes lipid soluble at physiologic pH

[10][2][15][16][17].

ABOUT

Special Considerations/Preparation

Injectable
Available: preservative-free 1- and 5-mg/mL concentrations in 1-, 2-, and 5-mL vials. Also available in an injectable form as 1- and 5-mg/mL concentrations in 1-, 2-, 5-, and 10-mL vials which contain 1% (10 mg/mL) benzyl alcohol as a preservative.
Stability:
Stable for 24 hours when diluted with NS or D_5W to a concentration of 0.5 mg/mL; stable for 4 hours in LR [2].
At least 95% of the initial concentration of midazolam remained on day 100 when midazolam 5 mg/mL and midazolam 0.4 mg/mL in D5W were stored at room temperature in polypropylene syringes [18].

Oral
Available: Oral syrup 2 mg/mL.
Storage: Store at room temperature [10].

Intranasal
Availability: Single-dose nasal spray unit delivers 5 mg of midazolam in 0.1 mL of solution.
Storage: Store at a controlled room temperature between 20 and 25 degrees C (68 to 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 to 86 degrees F) [9]

Other Routes
Injectable formulation was used for intranasal, buccal, or rectal administration [19][20][17].

DOSING/ADMINISTRATION

Dose

Low Cardiac Output; Post-Cardiac Surgery
Loading dose: 50 mcg/kg IV over 15 minutes [1] or 75 mcg/kg IV infused over 60 minutes, immediately followed by a maintenance infusion [2] has been used. In premature infants less than 30 weeks gestational age, infuse loading dose over 3 hours.
Maintenance infusion: 0.3 [3] to 0.75 mcg/kg/minute [2] for 35 hours [2].
Note: Above doses are from studies that included mostly older infants and children for the treatment or prevention of low cardiac output post-cardiac surgery.
Adjust infusion rate based upon hemodynamic and clinical response.

Uses

Low Cardiac Output Post-Cardiac Surgery; Prophylaxis: In one double-blind, placebo-controlled study (n=238) in children after cardiac surgery, the relative risk reduction for the prevention of low cardiac output syndrome was 55% (p=0.023) with milrinone (75 mcg/kg bolus, followed by 0.75 mcg/kg/minute infusion) compared with placebo. The age range was 2 days to 6.9 years (median, 3 months) [2]. A transient increase in heart rate (149+/-13 to 163+/-12 beats/min) was observed in 10 neonates administered 50 mcg/kg loading dose over 15 minutes; no neonate experienced sustained supraventricular tachyarrhythmias or ventricular ectopy [1].

Low Systemic Blood Flow, Prevention: A randomized, placebo-controlled clinical trial demonstrated milrinone was no more effective than placebo in preventing low systemic blood flow in **preterm neonates** less than 30 weeks GA. Neonates received milrinone (started before 6 hours of age) 0.75 mcg/kg/minute for the first 3 hours followed by 0.20 mcg/kg /minute until 18 hours of age. There was no difference in superior vena cava flow between the milrinone and placebo groups. A heart rate of 160 beats/min or more occurred in 67% of the milrinone-treated group and 22% of the placebo-treated group (p=0.0001) [6].

Persistent Pulmonary Hypertension of the Newborn (PPHN): Low level evidence exists for the use of milrinone for PPHN. The use of IV milrinone for infants with PPHN and signs of left ventricular dysfunction may be considered [7]. Typically, reserved for severe PPHN refractory to inhaled nitric oxide complicated by poor cardiac function on echocardiogram [8]. In 5 observational studies, term neonates (n=47) with oxygen index (OI) greater than 20 despite inhaled nitric oxide received IV milrinone. Improvements observed were OI reduction, inhaled nitric oxide dose reduction, and indicators of myocardial performance increase [9][10][11][12][13]. Transient nonsignificant decreases in systolic arterial pressure [10], as well as reductions in blood pressure requiring vasopressor inotropes have been observed [9]. Dose ranges were 0.33 to 0.99 mcg/kg/min with or without a bolus

dose of 50 mcg/kg over 60 minutes [9][10][11][12][13].

Severe Sepsis and Septic Shock[14]

<table>
<tr><td colspan="3">Hemodynamic Support - First 60 Minutes</td></tr>
<tr><td>Time</td><td colspan="2">Management- Proceed to next step if shock persists</td></tr>
<tr><td>0 minutes</td><td colspan="2">Maintain airway and establish access</td></tr>
<tr><td>5 minutes</td><td colspan="2">Push 10 mL/kg isotonic crystalloid or colloid boluses up to 40 mL/kg until improved perfusion or unless hepatomegaly.
Begin prostaglandin infusion until rule out ductal-dependent lesion.</td></tr>
<tr><td rowspan="2">15 minutes</td><td colspan="2">DOPamine less than 10 mcg/kg/min +/- DOBUTamine for fluid-refractory shock</td></tr>
<tr><td colspan="2">EPINEPHrine 0.05 to 0.3 mcg/kg/min for fluid-refractory DOPamine-resistant shock</td></tr>
<tr><td rowspan="4">60 min</td><td>Cold shock-Poor LV function
Normal blood pressure
ScvO(2) less than 70%*/Hgb greater than 12 g/dL
SVC flow less than 40 mL/kg/min or CI less than 3.3 L/min/m(2)</td><td>Add nitrovasodilator milrinone or inamrinone with volume loading</td></tr>
<tr><td>Cold shock- Poor RV function
PPHN
ScvO(2) less than 70%*
SVC flow less than 40 mL/kg/min or CI less than 3.3 L/min/m(2)</td><td>Inhaled nitric oxide
Inhaled iloprost or IV adenosine
IV milrinone or inamrinone</td></tr>
<tr><td>Warm shock- Low blood pressure</td><td>Titrate volume
Add norepinephrine
Vasopressin or terlipressin or angiotensin</td></tr>
<tr><td>Refractory shock</td><td>Hydrocortisone if absolute adrenal insufficiency.
Triiodothyronine if hypothyroid.
Begin pentoxifylline</td></tr>
</table>

		if VLBW newborn. Consider closing PDA if hemodynamically significant.
	ECMO	
Goals •First Hour: restore and maintain heart rate thresholds, capillary refill of 2 seconds or less, and normal blood pressure. • NICU: normal MAP-CVP, preductal and postductal oxygen saturation difference less than 5%, *ScvO(2) greater than 70% (except congenital heart patients with mixing lesions), SVC flow greater than 40 mL/kg/min, or cardiac index greater than 3.3 L/min/m(2)		
KEY: CI = cardiac index, Hgb = hemoglobin, LV function = left ventricle function, MAP-CVP = mean arterial pressure-central venous pressure, PDA = patent ductus arteriosus, PPHN = persistent pulmonary hypertension of the newborn, ScvO(2) = continuous central venous oxygen saturation, SVC = superior vena cava, VLBW = very low birth weight		
Davis et al: Crit Care Med 2017;45(6)		

Administration

•Administer loading dose over 10 to 60 minutes [4]. May give undiluted or further dilute in compatible diluent [5].
• In premature infants less than 30 weeks gestational age, infuse loading dose over 3 hours.
• For maintenance infusion, dilute in compatible solution to a **concentration of 200 mcg/mL**[5].
•May also be given by IO route if IV access unavailable [4] .

MEDICATION SAFETY

Contraindications/Precautions

Precautions
Cardiovascular: Ventricular and supraventricular arrhythmias, including nonsustained ventricular tachycardia, have been reported; increased risk in combination with other drugs; close monitoring recommended [5].
Cardiovascular: Slight shortening of AV node conduction time may occur, with potential for

increase in ventricular response rate, in patients with atrial fibrillation/flutter uncontrolled by digitalis [5].
Cardiovascular: Long-term oral or IV use exceeding 48 hours (unapproved use) for heart failure has not been demonstrated to be safe or effective; monitoring recommended [5].
Cardiovascular: Decrease in blood pressure may occur during therapy; monitoring recommended, slowing rate of infusion or discontinuation recommended if excessive decreases occur[5].
Cardiovascular: Outflow tract obstruction may be aggravated in patients with severe obstructive aortic or pulmonic valvular disease; use not recommended in place of surgical relief of obstruction [5].
Cardiovascular: Acute phase post myocardial infarction; use is not recommended [5].
Cardiovascular: Significant decreased cardiac filling pressure due to prior vigorous diuretic therapy; monitoring recommended [5]
Concomitant use: Improvement in cardiac output may potentiate effects of diuretic therapy; dose adjustment of diuretics may be necessary [5].
Endocrine and metabolic: Hypokalemia may occur due to excessive diuresis; increased risk of arrhythmias in digitalized patients; supplement potassium prior to and during use [5].

Adverse Effects

Assure adequate vascular volume prior to initiating therapy. Blood pressure will likely fall 5% to 9% after the loading dose, but should gradually return to baseline by 24 hours. Heart rate increases of 5% to 10% are also common. Thrombocytopenia was reported frequently in some studies and rarely in others. Arrhythmias occur occasionally.

Solution Compatibility

D_5W, NS, and LR.

Terminal Injection Site Compatibility

Acyclovir, amikacin, aminophylline, amiodarone, ampicillin, atracurium, atropine, bumetanide, calcium chloride, calcium gluconate, cefazolin, cefepime, cefotaxime, ceftazidime, cimetidine, clindamycin, dexamethasone, digoxin, dobutamine, dopamine, epinephrine, fentanyl, gentamicin, heparin, insulin, isoproterenol, lorazepam, meropenem, methylprednisolone, metronidazole, micafungin, midazolam, morphine, nicardipine, nitroglycerin, norepinephrine, oxacillin, pancuronium, piperacillin, piperacillin/tazobactam, potassium chloride, propofol, propranolol, ranitidine, sodium bicarbonate, sodium nitroprusside, theophylline, ticarcillin, ticarcillin/clavulanate, tobramycin, vancomycin, and vecuronium.

Terminal Injection Site Incompatibility

Furosemide, imipenem/cilastatin and procainamide.

Monitoring

•Monitor blood pressure, heart rate, and ECG continuously [5]
• Carefully monitor fluid and electrolyte changes, renal function [5]
•Infusion site (for extravasation) during therapy [5]..
•Monitor hemodynamic and clinical response[5].

For a full-term newborn, the target heart rate and perfusion pressure (mean arterial pressure minus central venous pressure) are 110 to 160 beats/min and 55 mm Hg, respectively [14].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action: Milrinone improves cardiac output by enhancing myocardial contractility, enhancing myocardial diastolic relaxation and decreasing vascular resistance. It acts via selective phosphodiesterase III inhibition that leads to increased intracellular cyclic AMP, increased myocardial intracellular calcium, and increased reuptake of calcium after systole. Vasodilatation is related to increased levels of cyclic GMP in vascular smooth muscle. Unlike catecholamines, myocardial oxygen consumption is not increased.

Distribution
Protein Binding: 70% bound to plasma protein [15].
Vd: 576 mL/kg in preterm (26 weeks gestational age (range, 23 to 28 weeks)) infants (first day of life) [16] and 560 mL/kg (0.56 L/kg) in 11 infants (mean gestation age 39.2 weeks) at 14 hours of age [10].

Elimination
Excretion: Primarily renally eliminated [15]
Clearance: 0.64 mL/kg/min in preterm (26 weeks gestational age (range, 23 to 28 weeks)) infants (first day of life) [16], 1.8 mL/kg/min (0.108 L/kg/hr) in 11 infants (mean gestation age 39.2 weeks) 14 hours of age with PPHN [10] and 3.05 mL/min/kg (7.65 mL/min/3.4 kg) in 6 infants with a median age of 2 days (1 to 9 days) (median gestational age 39 weeks) administered IV milrinone for persistent pulmonary hypertension of the newborn (PPHN) [17].
Half-life: 10.3 hours in preterm (26 weeks gestational age (range, 23 to 28 weeks)) infants (first day of life) [16] and 4.1 hours in 11 infants (mean gestation age 39.2 weeks) 14 hours of age [10].

Target Concentration and Dosages: Milrinone concentration of 150 to 200 ng/mL would be achieved 80% of the time with a bolus dose of 0.73 mcg/kg/min for 3 hours followed by 0.16 mcg/kg/min maintenance infusion in preterm neonates after surgical closure of patent ductus arteriosus in a simulation study [18]. A milrinone concentration of 180 to 300 ng/mL was achieved in 10 preterm infants who received 0.75 mcg/kg/min for 3 hours IV followed by 0.2 mcg/kg/min until 18 hours of age for the prevention of low systemic blood flow [16]. The steady state concentration of milrinone was 291 ng/mL in 11 infants (mean gestation age 39.2 weeks) 14 hours of age administered milrinone 50 mcg/kg IV over 60 minutes followed by a median dose of 0.33 mcg/kg/min for PPHN for 24 hours [10]

ABOUT

Special Considerations/Preparation

Available in 1-mg/mL solution for injection in 10-, 20-, and 50-mL single-dose vials. Dilute with compatible diluent prior to administration. **Maximum concentration for infusion is 200 mcg/mL.** Also available as premixed solution for injection (100-mL and 200-mL bags) in a concentration of 200 mcg/mL in 5% Dextrose (pH of 3.2 to 4) [19][15].

Morphine

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

0.05 to 0.2 mg/kg per dose IV, IM, or subQ.
Repeat as required (usually every 4 hours).

Opioid dependence: Begin at most recent IV morphine dose equivalent. Taper 10% to 20% per day as tolerated. Oral dose is approximately 3 to 5 times IV dose.

Pain
Continuous infusion: Loading dose 0.1 mg/kg IV followed by 0.01 mg/kg/hour [1][2][3][4]; postoperatively may be increased further to 0.02 mg/kg/hr [1].

Neonatal Abstinence Syndrome
Initial dose: 0.03 to 0.1 mg/kg per dose orally every 3 to 4 hours. **Maximum dose 0.2 mg/kg**[5][6][7]. Wean dose by 10% to 20% every 2 to 3 days based on abstinence scoring [8][9][7].

Dosage Adjustment
Hypothermia, Therapeutic: Dose reduction of morphine administered for comfort and analgesia may be necessary in neonates with hypoxic ischemic encephalopathy receiving hypothermia therapy [10]. Dose simulations predicted morphine concentrations of 10 to 40 nanograms/mL in full-term neonates [11][10] receiving a 0.05 mg/kg IV loading dose followed by [11] continuous morphine infusion of 0.005 mg/kg/hr IV [11][10] or an intermittent dose of 0.04 to 0.05 mg/kg/dose IV every 6 hours and a concentration of 10 nanograms/mL with 0.0025 mg/kg/hr continuous IV dosing [10]. Due to large inter-patient variability, doses may need to be increased or decreased [11].

Uses

Analgesia: There is insufficient evidence to support the routine use of opioids in mechanically ventilated neonates to reduce pain in a systematic review (n=13 studies; 1505 neonates) [15][16].

Neonatal abstinence syndrome (NAS)[17][5].
Sublingual buprenorphine was associated with the largest reduction in length of treatment and length of stay for NAS in a network meta-analysis of 18 randomized controlled trials (n=1072) of buprenorphine, clonidine, diluted tincture of opium and clonidine, diluted tincture of opium, morphine, methadone, and phenobarbital. Morphine was the least effective opioid [18]. The findings should be interpreted with caution due to significant study limitations [18][19]

Compared with buprenorphine: Sublingual buprenorphine reduced the duration of treatment for neonatal abstinence syndrome compared with oral morphine (15 days vs 28 days; p less than 0.001) in a double-blind, double-dummy, single-center study (n=63). Preterm infants and infants exposed to benzodiazepines in utero were excluded. Median length of hospital stay was 21 vs 33 days (p less than 0.001) and use of supplemental phenobarbital was 15% vs 23% (p=0.36) for buprenorphine and morphine, respectively. Rates of adverse events were not different between the 2 groups [20]

Compared with methadone: Methadone outperformed morphine for the treatment of NAS in a multicenter, randomized, double-blind study of 116 term infants (median length of hospital stay (LOS) (16 vs 20 days, p=0.005), LOS attributable to NAS (16 vs 19 days, p=0.005), and length of drug treatment (11.5 vs 15 days, p=0.009)). Initial oral doses were 0.3 mg/kg/day for Finnegan score (FS) of 8 to 10, 0.5 mg/kg/day for FS of 11 to 13, 0.7 mg/kg/day for FS 14 to 16, and 0.9 mg/kg/day for FS of 17 or more. The total daily doses were divided every 4 hours for morphine and every 8 hours for methadone. A nonalcoholic solution of methadone was compounded [17].

Neonatal abstinence syndrome was treated for a median of 14 days with methadone compared with 21 days for morphine (p=0.008) in a double-blind, randomized trial (n=78). All neonates were 35 weeks gestational or more and prenatal exposure was either methadone or buprenorphine [21].

Compared with cloNIDine: Overall, cloNIDine monotherapy for NAS appeared to be as effective as morphine in a randomized, double-blind, pilot study of 31 neonates younger than 7 days (gestational age, 35 weeks or more). Rescue drugs were not necessary in any neonate. The initial cloNIDine dose was 0.625 mcg/kg/dose orally every 3 hours with dose titrations up to a maximum of 12 mcg/kg/day [22].

Opioid dependence [5][9].

Procedural Pain: Morphine 100 mcg/kg orally administered 60 minutes prior to retinopathy of prematurity screening in non-ventilated premature (less than 32 weeks' gestation or with a birthweight of less than 1501 g) infants produced adverse cardiorespiratory effects for an average of 6 to 8 hours in a randomized blinded placebo-controlled trial (n=31). The study was underpowered (early termination due to safety findings) to detect differences in efficacy between morphine and placebo. Oxygen desaturation at 6 and 24 hours after procedure and bradycardia episodes at 24 hours after procedure occurred significantly more in the morphine-group than placebo-group. Apneic episodes requiring resuscitation with non-invasive positive pressure ventilation within the 24 hours after administration occurred in 20% of the morphine-group and 0% in the placebo-group [23].

Sedation.

Administration

IV: The recommended standard concentrations of morphine solutions are 0.1 mg/mL for continuous infusion and 0.1 and 0.5 mg/mL for intermittent infusions. Typically, morphine intermittent infusion is administered over 15 to 30 minutes [12]. Intermittent morphine was infused over 1 hour in some studies [13][14].

MEDICATION SAFETY

Contraindications/Precautions

Contraindications

Significant respiratory depression [25]
Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment [25]
Concomitant use with MAOIs, or use of MAOIs within 14 days [25]
Known or suspected gastrointestinal obstruction, including paralytic ileus [25]
Hypersensitivity (eg, anaphylaxis) to morphine [25]
Neuraxial administration contraindications include: infection at injection microinfusion site, concomitant anticoagulant therapy, uncontrolled bleeding diathesis, or the presence of any other concomitant therapy or medical condition which would render epidural or intrathecal administration of medication especially hazardous [25].

Precautions

Cardiovascular: Avoid use in patients with circulatory shock; further reduction in cardiac output or blood pressure may occur [25].
Cardiovascular: Severe hypotension, including orthostatic hypotension and syncope in ambulatory patients may occur; especially in patients with compromised ability to maintain blood pressure; monitoring recommended [25]
Cardiovascular: Orthostatic hypotension may occur with single-dose neuraxial morphine analgesia; monitoring recommended in ambulatory patients with reduced circulating blood volume, impaired myocardial function or on sympatholytic drugs [25].
Concomitant use: Avoid use with mixed agonist/antagonist or partial agonist analgesics (eg, pentazocine, nalbuphine, butorphanol, buprenorphine) as withdrawal symptoms may occur [25]
Endocrine and metabolic: Adrenal insufficiency has been reported with opioid use. If adrenal insufficiency is suspected, perform diagnostic testing, treat with corticosteroids if confirmed, wean patient off of opioid if appropriate, and continue to assess adrenal function [25].
Gastrointestinal: Difficulty with swallowing may occur due to Arymo(R) ER tablet stickiness and swelling, including choking, gagging, regurgitation, and having a tablet stuck in the throat. Do not presoak, lick, or wet tablets prior to use. Take tablets singly and immediately after placing in the mouth with enough water to ensure complete swallowing; alternative therapy may be required [30].
Gastrointestinal: Intestinal obstruction or exacerbation of diverticulitis may occur due to Arymo(R) ER tablet stickiness and swelling, especially in patients with underlying gastrointestinal disorders such as esophageal cancer or colon cancer with a small gastrointestinal lumen; alternative therapy may be required [30].
Hepatic: Spasm of the sphincter of Oddi may occur; monitoring recommended in patients with biliary tract disease, including acute pancreatitis [25]
Hepatic: Use caution with epidural administration in patients with hepatic dysfunction [25].
Hepatic: Respiratory depression, sedation, and hypotension may occur in patients with cirrhosis; monitoring recommended [27]
IV administration: Use caution when injecting intramuscularly into chilled areas or in

patients with hypotension or shock, since impaired perfusion may prevent complete absorption. If repeated injections are administered, an excessive amount may be suddenly absorbed if normal circulation is re-established [31].
IV administration: Rapid intravenous administration may result in chest wall rigidity [32].
Neurologic: Potentially life-threatening serotonin syndrome may occur, particularly with concomitant use of serotonergic drugs [33].
Neurologic: Use caution in patients susceptible to intracranial effects of carbon dioxide retention (eg, those with brain tumors or increased intracranial pressure) as reduced respiratory drive may occur, further increasing intracranial pressure; monitoring recommended [25]
Neurologic: Opioids may obscure the clinical course in patients with head injury [25].
Neurologic: Avoid use in patients with impaired consciousness or coma [25].
Neurologic: Myoclonic-like spasm of lower extremities has been reported with intrathecal doses of more than 20 mg/day [25].
Neurologic: Seizure disorders may be induced or aggravated; monitoring recommended [25]
Neurologic: Excitation of the central nervous system, resulting in convulsions, may accompany high doses of morphine given intravenously [32].
Neurologic: Inflammatory masses such as granulomas, some of which have resulted in serious neurologic impairment including paralysis, have been reported in patients receiving continuous infusion of opioids via indwelling intrathecal catheter; monitoring recommended [25].
Neurologic: Opioid-induced hyperalgesia (OIH) may occur and has been reported with short-term and longer-term use of opioid analgesics; dosage adjustment or opioid rotation (safely switching to a different opioid moiety) may be necessary [25].
Prolonged use: Long-term use of opioids may be associated with decreased sex hormone levels and symptoms such as reduced interest in sex, impotence, or infertility. Laboratory evaluation may be warranted [33].
Renal: Urinary retention, which may persist 10 to 20 hours following single epidural or intrathecal administration, is a frequently associated with neuraxial opioid administration, more frequently in male patients than female patients. Urinary retention may also occur during the first several days of hospitalization for the initiation of continuous intrathecal or epidural morphine therapy; monitoring recommended and prompt intervention required [25].
Renal: Respiratory depression, sedation, and hypotension may occur in patients with renal failure; monitoring recommended [25]
Renal: Use caution with epidural administration in patients with renal dysfunction [25].
Respiratory: Sleep-related breathing disorders including central sleep apnea and sleep-related hypoxemia may occur and risk increases in a dose-dependent fashion; dose reduction may be necessary [25].
Respiratory: Patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, especially during treatment initiation and titration; monitoring recommended, particularly during treatment initiation and titration or when using concomitant drugs that depress respiration; may consider non-opioid therapy [25]
Respiratory: Severe respiratory depression up to 24 hours following epidural or intrathecal administration has been reported [25]; single-dose neuraxial administration may result in acute or delayed respiratory depression for periods at least as long as 24 hours [32].
Special populations: Elderly, cachectic, or debilitated patients are at increased risk for respiratory depression, especially during treatment initiation and titration; monitoring

recommended, particularly during treatment initiation and titration or when using concomitant drugs that depress respiration; may consider non-opioid therapy [25]
Special populations: Neonatal opioid withdrawal syndrome, which may be life-threatening, may occur after prolonged use during pregnancy; monitor newborn and treat appropriately [25].
Withdrawal: Serious withdrawal symptoms may occur upon sudden dose decrease or discontinuation in patients who are physically dependent on opioids; do not discontinue abruptly and create a patient-specific plan to taper gradually [25]

Adverse Effects

Naloxone should be readily available to reverse adverse effects. Marked respiratory depression (decreases the responsiveness of the respiratory center to CO_2 tension). Hypotension and bradycardia. Transient hypertonia. Ileus and delayed gastric emptying. Urine retention. Tolerance may develop after prolonged use; wean slowly. Seizures reported in two infants who received bolus plus infusion.

Black Box Warning

Injection route, solution
•*Risks with Neuroaxial Administration:* Single-dose neuraxial administration may result in acute or delayed respiratory depression up to 24 hours. Because of the risk of severe adverse reactions when morphine sulfate is administered by the epidural or intrathecal route of administration, patients must be observed in a fully equipped and staffed environment for at least 24 hours after the initial dose
•*Life-Threatening Respiratory Depression:* Serious, life-threatening, or fatal respiratory depression may occur with use of morphine sulfate bitartrate, especially during initiation or following a dosage increase. To reduce the risk of respiratory depression, proper dosing and titration of morphine sulfate are essential [25].
•*Addiction, Abuse, and Misuse:* Because the use of morphine sulfate exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death, assess each patient's risk prior to prescribing and reassess all patients regularly for the development of these behaviors or conditions [25].
Neonatal Opioid Withdrawal Syndrome: If opioid use is required for an extended period of time in a pregnant woman, advise the patient of the risk of NOWS, which may be life-threatening if not recognized and treated. Ensure that management by neonatology experts will be available at delivery [25].
Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants: Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of morphine sulfate and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate [25].

Oral route

•*Risk of Medication Errors:* Ensure accuracy when prescribing, dispensing, and administering morphine sulfate oral solution. Dosing errors due to confusion between mg and mL, and other morphine solutions of different concentrations can result in accidental overdose and death [26].
•*Addiction, Abuse, and Misuse:* Because the use of morphine sulfate exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death, assess each patient's risk prior to prescribing and reassess all patients regularly for the development of these behaviors or conditions [27].
•*Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS):* Healthcare providers are strongly encouraged to complete a REMS-compliant education program and to counsel patients and caregivers on serious risks, safe use, and the importance of reading the Medication Guide with each prescription.
•*Life-Threatening Respiratory Depression:* Serious, life-threatening, or fatal respiratory depression may occur with use of morphine sulfate, especially during initiation or following a dosage increase. To reduce the risk of respiratory depression, proper dosing and titration of morphine sulfate are essential. Instruct patients to swallow morphine sulfate tablets whole; crushing, chewing, or dissolving morphine sulfate tablets can cause rapid release and absorption of a potentially fatal dose of morphine [27].
•*Accidental Ingestion:* Accidental ingestion of morphine sulfate, especially in children, can result in a fatal overdose [27].
•*Neonatal Opioid Withdrawal Syndrome:* If opioid use is required for an extended period of time in a pregnant woman, advise the patient of the risk of NOWS, which may be life-threatening if not recognized and treated. Ensure that management by neonatology experts will be available at delivery [27].
•*Interaction with Alcohol:* Instruct patients not to consume alcoholic beverages or use prescription or nonprescription products that contain alcohol while taking morphine sulfate. The co-ingestion of alcohol with morphine sulfate may result in increased plasma levels and a potentially fatal overdose of morphine[28].
•*Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants:* Concomitant use of opioids and benzodiazepines or other CNS depressants may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of morphine sulfate and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate [27].

Rectal, suppositories[29]
Morphine sulfate suppositories expose users to risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess patient’s risk before prescribing and monitor regularly for these behaviors or conditions.
Serious, life-threatening , or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase
Accidental exposure of morphine sulfate suppositories, especially by children, can result in a fatal overdose of opium
Prolonged use of morphine sulfate suppositories during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and

follow patients for signs and symptoms of respiratory depression and sedation.

Solution Compatibility

D_5W, $D_{10}W$, and NS.
For continuous infusions of morphine **containing heparin:** Use only NS; maximum morphine concentration 5 mg/mL.

Terminal Injection Site Compatibility

Acyclovir, alteplase, amikacin, aminophylline, amiodarone, ampicillin, atropine, aztreonam, bumetanide, caffeine citrate, calcium chloride, caspofungin, cefotaxime, cefoxitin, ceftazidime, ceftriaxone, chloramphenicol, cefazolin, cimetidine, clindamycin, dexamethasone, digoxin, dobutamine, dopamine, enalaprilat, epinephrine, erythromycin lactobionate, esmolol, famotidine, fentanyl, fluconazole, furosemide, gentamicin, glycopyrrolate, heparin, hydrocortisone succinate, ibuprofen lysine, insulin, lidocaine, linezolid, lorazepam, meropenem, metoclopramide, metronidazole, mezlocillin, midazolam, milrinone, nafcillin, nicardipine, nitroglycerin, oxacillin, pancuronium bromide, penicillin G, phenobarbital, piperacillin, piperacillin/tazobactam, potassium chloride, propofol, propranolol, ranitidine, remifentanil, sodium bicarbonate, sodium nitroprusside, ticarcillin/clavulanate, tobramycin, trimethoprim/sulfamethoxazole, vancomycin, vecuronium, and zidovudine.

Terminal Injection Site Incompatibility

Azithromycin, cefepime, micafungin, pentobarbital, and phenytoin.

Monitoring

Monitor respiratory and cardiovascular status closely. Observe for abdominal distention and loss of bowel sounds. Consider urine retention if output is decreased. For infants experiencing neonatal abstinence syndrome, monitor and score signs of drug withdrawal using a published abstinence assessment tool such as the modified Neonatal Abstinence Scoring System (Finnegan) or the Lipsitz tool [5][9].
Monitor patients susceptible to the intracranial effects of carbon dioxide retention (eg, evidence of intracranial pressure or brain tumors) for signs and symptoms of sedation and respiratory depression, particularly during initiation of therapy [24].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action: Morphine is a narcotic analgesic that stimulates brain opioid receptors. Increases venous capacitance, caused by release of histamine and central suppression of adrenergic tone. GI secretions and motility decreased. Increases smooth muscle tone [34].

Pharmacokinetics are widely variable, including a more than 4-fold variation in morphine exposure in neonates (gestational age 36 to 41.3 weeks; median 39 weeks) with hypoxic ischemic encephalopathy receiving hypothermia therapy [10].
Bioavailability: Morphine is 20% to 40% bioavailable when administered orally.
Vd: In 20 neonates (gestational age 36 to 41.3 weeks) with hypoxic ischemic encephalopathy (HIE) receiving **hypothermia therapy**, morphine Vd was 8.02 L (coefficient of variation, 49%) [10]
Metabolism: Morphine is converted in the liver to two glucuronide metabolites (morphine-6-glucuronide and morphine-3-glucuronide) that are renally excreted. Morphine-6-glucuronide (M6G) is a potent respiratory-depressant and analgesic. Morphine-3-glucuronide (M3G) is an antagonist to the effects of morphine and morphine-6-glucuronide.
Clearance: In 20 neonates (gestational age 36 to 41.3 weeks) with hypoxic ischemic encephalopathy (HIE) receiving **hypothermia therapy**, morphine clearance was 0.765 L/hr +/- 10.9%. This was considered markedly lower compared with full-term normothermic neonates younger than 7 days without HIE in other studies [10]
Half-life: Approximately 9 hours for morphine and 18 hours for morphine-6-glucuronide. Steady state concentrations of morphine are reached by 24 to 48 hours.

Hypothermia: In neonates with hypoxic ischemic encephalopathy receiving hypothermia therapy, morphine 2.5 mcg/kg/hr was predicted to achieve a concentration of 10 nanograms/mL [10], in contrast to a dose of 5 mcg/kg/hr at birth (term neonates, 3.3 kg) and 8.5 mcg/kg/hr at 1 month (4 kg) in infants who underwent noncardiac surgery [35].

Surgery: In a pharmacokinetic analysis of 184 pediatric patients 0 to 3 years of age who underwent noncardiac surgery and received morphine IV postoperatively, the Vd (L per 70 kg) was 84 at birth, 92 at 7 days, 112 at 30 days, 131 at 90 days, and 136 for older than 90 days up to 3 years. The clearance (L/hr per 70 kg) for the parent drug was 14.5 at birth, 17.4 at 7 days, 26.3 at 30 days, 43.1 at 90 days, 57.3 at 180 days, 67.8 at 365 days, and 71.1 at 1000 days. A predicted mean steady serum concentration of 10 nanogram/mL for morphine may be achieved with morphine hydrochloride infusion at rates of 5 mcg/kg/hr at birth (term neonates, 3.3 kg), 8.5 mcg/kg/hr at 1 month (4 kg), 13.5 mcg/kg/hr at 3 months (6 kg), 18 mcg/kg/hr at 1 year (10 kg), and 16 mcg/kg/hr for children 1 to 3 years of age (12 to 18 kg) [35].

ABOUT

Special Considerations/Preparation

Available

Injection: Strengths ranging from 0.5 to 50 mg/mL.
Stability: At least 95% of the initial concentration of morphine remained on day 100 when morphine 1 mg/mL in NS or D5W was stored at room temperature in polypropylene syringes [36].

Oral

Available: 2, 4, and alcohol-free 20 mg/mL oral morphine sulfate solutions. The 20 mg/mL (100 mg/5 mL) oral solution is for use **only** in opioid-tolerant patients [37][37]. Available in immediate-release tablets (15 mg and 30 mg) and various extended-release tablet and capsule formulations (10 to 200 mg).

Extemporaneous Oral Solution

A 0.2 mg/mL oral morphine solution prepared with morphine elixir 2 mg/mL diluted with distilled water and stored in amber, plastic syringes at 25° C was stable for 60 days[38].
A 0.4 mg/mL oral morphine solution may be made by diluting 2 mL of alcohol-free oral morphine sulfate solution (2 mg/mL) in 8 mL of sterile water for irrigation. The solution is stable for 60 days under room temperature. Protect from light [39].

Moxifloxacin

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Ophthalmic
Bacterial Conjunctivitis
Vigamox®
Instill 1 drop into the affected eye 3 times daily for 7 days [1].

Uses

Pediatric FDA-Approved Indications
Ophthalmic
Treatment of bacterial conjunctivitis caused by susceptible strains of the following organisms: *Corynebacterium species, Micrococcus luteus, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Staphylococcus hominis, Staphylococcus warneri, Streptococcus pneumoniae, Streptococcus viridans group, Acinetobacter lwoffii, Haemophilus influenzae, Haemophilus parainfluenzae*, and *Chlamydia trachomatis*[1].

Administration

Ophthalmic
For topical ophthalmic use only. Do not inject subconjunctivally or introduce directly into the anterior chamber of the eye [1].

MEDICATION SAFETY

Contraindications/Precautions

Hypersensitivity reaction may occur. Discontinue at first sign [1].
Prolonged use may result in overgrowth of nonsusceptible organisms [1].

Adverse Effects

Ophthalmic: The most frequently reported adverse events were conjunctivitis, decreased visual acuity, keratitis, dry eye, ocular discomfort, ocular hyperemia, ocular pain, ocular pruritus, subconjunctival hemorrhage, and tearing. Nonocular-related adverse events included fever, increased cough, infection, otitis media, pharyngitis, rash, and rhinitis [1].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Ophthalmic
Mechanism of action
Moxifloxacin, a fluoroquinolone, has a mechanism of action that is different from macrolides, aminoglycosides, and tetracyclines and may be active against pathogens that are resistant to these antibiotics. There is no cross-resistance between moxifloxacin and these classes of antibiotics; however, cross-resistance has been seen between systemic moxifloxacin and some other quinolones [1].

ABOUT

Special Considerations/Preparation

Ophthalmic:
Availability: Available as 0.5% strength, with 3 mL in a 4-mL bottle [1].
Storage: Store between 2 and 25 degrees C (36 and 77 degrees F) [1].

Mupirocin

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Cutaneous infections: Apply small amounts topically to affected areas 3 times daily.

Decolonization: Apply small amounts to anterior nares twice daily for 5 to 7 days.

Uses

Decolonization: Along with other infection control processes in a neonatal intensive care unit (NICU), mupirocin decolonization may be used during outbreaks of *Staphylococcus aureus* and in the management of colonized neonates at high risk for *S aureus* infection [1]. In a retrospective cohort study in a single-institution NICU (with low-level endemic MRSA), 22% (95% CI 4% to 37%) of MRSA acquisition could be attributed to MRSA carriers who were untreated [2]. Decolonization, which included intranasal mupirocin, of MRSA-colonized neonates (n=522) decreased the risk of gram-positive infections with no increased risk of gram-negative infection in a multicenter, retrospective NICU study [3].

Topical use for skin infections caused by *Staphylococcus aureus, S epidermidis, S saprophyticus,* and *Streptococcus pyogenes.*

MEDICATION SAFETY

Contraindications/Precautions

Use of Bactroban(R) ointment is not recommended with conditions in which absorption of large quantities of polyethylene glycol may occur, particularly in the presence of moderate or severe renal impairment [4]. Bactroban(R) ointment and cream are not for use on mucosal surfaces [4][5]. Discontinue use if sensitization or severe local irritation occur. Avoid contact with eyes and rinse thoroughly if accidental contact occurs [4][6][5].
Systemic allergic reactions, which may be severe, have been reported, including anaphylaxis, urticaria, angioedema, and rash [7].
Overgrowth of nonsusceptible organisms, including fungi, may occur with prolonged use. Clostridium difficile-associated diarrhea has been reported; evaluate and institute appropriate medical management if suspected or confirmed. Discontinuation may be warranted [4][6][5].
Avoid use of mupirocin nasal ointment with other intranasal products [6].

Adverse Effects

Use only on the skin. No adverse effects reported from topical administration. Routine use may lead to selective bacterial resistance.

Monitoring

Assess affected area for continued infection.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Topical antibacterial produced by fermentation of the organism *Pseudomonas fluorescens.* Inhibits protein synthesis by bonding to bacterial isoleucyl-transfer-RNA synthetase. Highly protein bound. Not absorbed into the systemic circulation after topical administration (older infants and children). Metabolized in the skin to an inactive compound and excreted.

ABOUT

Special Considerations/Preparation

Available in unit-dose packets and 15 and 30-g tubes as a 2% ointment and cream (20 mg/g).

Nafcillin

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Usual dosage: 25 mg/kg/dose IV.
Meningitis: 50 mg/kg/dose IV.

Antibiotic Dosing Chart:
Renal function and drug elimination are most strongly correlated with Postmenstrual Age (PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.

Dosing Interval Chart		
PMA (weeks)	**PostNatal (days)**	**Interval (hours)**
≤29	0 to 28 >28	12 8
30 to 36	0 to 14 >14	12 8
37 to 44	0 to 7 >7	12 8
≥45	ALL	6

Uses

Penicillinase-producing staphylococci infections, particularly if evidence of renal dysfunction.

Infective endocarditis: The following recommendations are based on a consensus of experts [3]. The full pediatric guidelines can be found here: https://doi.org/10.1161/CIR.0000000000000298

Organism Directed Therapy		
Organism	First-Choice	Alternative Choice
Streptococci		
Highly susceptible to penicillin G (MBC 0.1 mcg/mL or less); includes most viridans streptococci,	Penicillin G or CefTRIAXone	Vancomycin or First-generation cephalosporin or CefTRIAXone

groups A, B, C, G nonenterococcal, group D streptococci (S bovis, S equinus)		
Relatively resistant to penicillin (MBC 0.2 mcg/mL or more); less-susceptible viridans streptococci or enterococci	Penicillin G or Ampicillin + Gentamicin (for first 2 weeks, or entire course for enterococci)	Vancomycin + Gentamicin for enterococci Ampicillin + CefTRIAXone (for aminoglycoside (AMG)-resistant enterococci or AMG-intolerant patient) CefTRIAXone + gentamicin (not for enterococcal endocarditis)
Resistant to penicillin	Consult an infectious disease specialist.	---
Staphylococci (S aureus or coagulase-negative staphylococci) †		
Penicillin G susceptible (1 mcg/mL or less) (rare)	Penicillin G	Oxacillin or Nafcillin or First-generation cephalosporin or Vancomycin
Penicillin G resistant (0.1 mcg/mL)	Oxacillin or Nafcillin with or without Gentamicin	Vancomycin (for those highly allergic to beta-lactam antibiotics) or First-generation cephalosporin
Oxacillin (MRSA) resistant (4 mcg/mL)	Vancomycin	Daptomycin for right-sided endocarditis, maybe for left-sided
Vancomycin resistant or intolerant	Daptomycin	Unknown

	†When prosthetic material present add riFAMpin + gentamicin (for first 2 weeks) for all staphylococci	
Gram-negative enteric bacilli	CefTAZidime or Cefepime or Cefotaxime or CefTRIAXone Plus gentamicin (or tobramycin or amikacin, depending on susceptibility)	Broad-spectrum penicillin Plus gentamicin (or tobramycin or amikacin)
HACEK group	CefTRIAXone or Cefotaxime or Ampicillin-sulbactam	Ampicillin (when susceptible) Plus aminoglycoside
KEY: AMG = aminoglycosides; HACEK = Haemophilus species, Aggregatibacter species, Cardiobacterium hominis, Eikenella corrodens, and Kingella species; MBC = minimum bactericidal concentration, MRSA = methicillin-resistant Staphylococcus aureus (includes resistance to oxacillin, nafcillin, and cephalosporins)		
Baltimore, 2015		

Administration

Intravenous: Dilute dose with sterile water for injection or NS to a concentration of 40 mg/mL and administer over 5 to 10 minutes or dilute to a concentration of 20 to 40 mg/mL and infuse over 30 to 60 minutes [1][2].

MEDICATION SAFETY

Contraindications/Precautions

Increase dosing interval in patients with hepatic dysfunction. Irritating to veins; watch for phlebitis.

Adverse Effects

Cases of granulocytopenia have been reported.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Acyclovir, aminophylline, atropine, chloramphenicol, cimetidine, dexamethasone, enalaprilat, esmolol, famotidine, fentanyl, fluconazole, heparin, lidocaine, magnesium sulfate, morphine, nicardipine, potassium chloride, propofol, sodium bicarbonate, tobramycin, and zidovudine.

Terminal Injection Site Incompatibility

Amikacin, aztreonam, gentamicin, hydrocortisone succinate, insulin, methylprednisolone, midazolam, netilmicin, and vancomycin.

Monitoring

Observe IV site for signs of phlebitis and extravasation. Assess CBC, renal and hepatic function weekly in patients receiving long-term therapy [2][4].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Inhibits synthesis of bacterial cell wall. Better penetration into CSF than methicillin. Excreted via hepatic clearance.

ABOUT

Special Considerations/Preparation

Available in 1 and 2-g vials. Reconstitute 1-g vial with 3.4 mL of sterile water for injection to provide a final volume of 4 mL and a concentration of 250 mg/mL. Also available in 1-g in 50-mL and 2-g in 100-mL frozen single-dose bags. Thaw bags at room temperature or under refrigeration. Do not force thaw by immersing into water baths or microwaving. pH of resulting solution 6 to 8.5. Thawed solution stable for 3 days at room temperature, 21 days refrigerator. Reconstituted solution stable for 3 days at room temperature, 7 days refrigerated. Osmolality was determined to be 709 mOsm/kg of water. For direct intravenous injection, dilute in 15 to 30 mL of NS.

Naloxone

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

KIDs List: Avoid in neonates for postpartum resuscitation due to risk of seizure [1]
Resuscitation- Full Opioid Reversal (PALS guidelines)
0.1 mg/kg IV/intraosseous [2].
Naloxone is not recommended as part of the initial resuscitation of newborns with respiratory depression in the delivery room[3][4].
FDA Dosage
Usual dose: Initial, 0.01 mg/kg IV/IM/subQ; repeat every 2 to 3 minutes to the desired degree of reversal [5].
Repeat doses may be required at 1 to 2 hour intervals depending upon the amount, type of opioid (i.e., short or long acting), and time interval since last administration of an opioid. A longer lasting effect may be achieved with IM administration. Larger than necessary dosage of naloxone may result in significant reversal of analgesia and increase in blood pressure; too rapid reversal may induce nausea, vomiting, sweating or circulatory stress [5].

Emergency Treatment of Known or Suspected Opioid Overdose
Injection solution (Zimhi™): Initial, 5 mg (1 dose) IM or subQ injection into the anterolateral aspect of the thigh. Use a new Zimhi™ prefilled syringe if additional doses may be required. May repeat every 2 to 3 minutes. Higher or repeat doses may be required for reversal of partial agonists or mixed agonist/antagonists [6]
Nasal spray
Alternate naloxone-containing product may be preferable.
4 mg nasal spray: Initial, 1 spray intranasally into 1 nostril. Use a new naloxone nasal spray for subsequent doses and administer into alternating nostrils. May repeat every 2 to 3 minutes [7]. Higher or repeat doses may be required for reversal of partial agonists or mixed agonist/antagonists such as buprenorphine and pentazocine (FDA dosage) [7]
8 mg nasal spray (Kloxxado™): Initial, 1 spray (8 mg) intranasally into 1 nostril. If response not obtained after 2 or 3 minutes, use a new nasal spray for subsequent doses and administer into alternating nostrils. May repeat every 2 to 3 minutes. Repeat doses may be required for reversal of partial agonists or mixed agonist/antagonists [8]

Opioid Depression (associated with therapeutic opioid use): 0.001 to 0.005 mg/kg IV; titrate to effect (guideline dosage) [2].

Dose Adjustments
Renal adjustments: No specific recommendations are available [7][9][6][8][10][5].
Hepatic adjustments: No specific recommendations are available [7][9][6][8][10][5].

Uses

Resuscitation: Adjuvant therapy to customary resuscitation efforts for narcotic-induced respiratory (CNS) depression. Naloxone is not recommended as part of the initial resuscitation of newborns with respiratory depression in the delivery room. Before naloxone is given, providers should restore heart rate and color by supporting ventilation [4]. The American Heart Association (AHA) did not review the use of naloxone in the 2015 Neonatal Resuscitation guidelines; therefore, the 2010 AHA guidelines still apply [3].

Pediatric FDA Approved Indications
Injection: Naloxone is indicated for partial or complete reversal of opioid depression induced by natural or synthetic opioids, such as methadone, and certain mixed agonist-antagonist analgesics, including nalbuphine, pentazocine, butorphanol, and cyclazocine. The clinical response to naloxone may be incomplete or higher doses may be required for respiratory depression caused by partial agonists or mixed agonist/antagonists, such as buprenorphine or pentazocine. Naloxone injection is also indicated for the diagnosis of known or suspected acute opioid overdose [11]
Zimhi™ Injection Solution: Indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression, for adult and pediatric patients. It is intended for immediate administration as emergency therapy in settings where opioids may be present and not a substitute for emergency medical care [6]
Nasal Spray: Indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression, for adult and pediatric patients. It is intended for immediate administration as emergency therapy in settings where opioids may be present and not a substitute for emergency medical care [8][12][7]. The clinical response to naloxone may be incomplete or higher doses may be required for respiratory depression caused by partial agonists or mixed agonist/antagonists, such as buprenorphine or pentazocine [7].
In settings such as in neonates with known or suspected exposure to maternal opioid use, when it may be preferable to avoid the abrupt precipitation of opioid withdrawal symptoms, consider use of an alternate-containing product that can be dosed according to weight and titrated to effect. Also, in situations where the primary concern is for infants at risk for opioid overdose, consider whether the availability of alternate naloxone-containing products may be better suited than naloxone nasal spray [12]

Administration

Injection
Recommended route is IV push. Alternative routes are IM, subQ, [5] and intraosseous a [2]. May be diluted [5]

Zimhi™
IM or subQ Injection
• Zimhi™ is intended to be administered by individuals 12 years of age and older; younger patients or those with limited hand strength may have difficulty using device [6].
• Inject into the anterolateral aspect of the thigh with the needle facing downwards; inject through clothing if necessary [6].
• In pediatric patients under the age of one, the caregiver should pinch the thigh muscle

while administering dose [6].
• Embed the needle completely before transferring the thumb to the syringe plunger. Push the plunger all the way down until it clicks and hold for 2 seconds [6].
• Immediately after injection, using one hand with fingers behind the needle, slide the safety guard over the needle. Do not use two hands to activate the safety guard [6].
• Never put thumb, fingers, or hand over the exposed needle. Failure to follow these instructions may result in a needlestick injury; if an accidental needlestick occurs, get help immediately [6].
• Do not attempt to re-cap the needle with the needle cap once it has been removed [6].
• Place the patient in the lateral recumbent position (recovery position) [6].
• Put the used syringe into the blue case, close the case, and give your used prefilled syringe to the healthcare provider for inspection and proper disposal [6].
• Do not attempt to reuse, each prefilled syringe contains a single dose [6].

Nasal route
• Patient should be in a supine position for administration [8][7].
• Do not prime or test the device prior to use [8][7].
• Press firmly on device plunger to administer dose and remove device nozzle from nostril after use [8][7][9].
• Administer into alternate nostrils with each dose [8][7].
• Do not reuse a naloxone nasal spray; use a new nasal spray for each dose [8][7][9].
• Turn patient onto their side after administration of the first dose [8][7].

MEDICATION SAFETY

Contraindications/Precautions

Precautions
May result in acute abstinence syndrome, manifested as convulsions, excessive crying, and hyperactive reflexes. Opioid withdrawal may be life-threatening in neonates [13]. Recurrence of respiratory and/or CNS depression may occur following an initial improvement in symptoms [14].
Accidental injury: Accidental needlestick injury may occur; medical attention may be necessary [6]
Neurologic: CNS depression may return after initial symptomatic improvement; seek emergency assistance immediately after first dose, provide continued surveillance, and repeat dose as necessary. Additional supportive and resuscitative measures may be necessary while awaiting medical assistance [8].
Psychiatric: Agitation has been reported with excessive doses that may result in significant reversal of analgesia [8][6].
Respiratory: Respiratory depression may return after initial symptomatic improvement; seek emergency assistance immediately after first dose, provide continued surveillance, and repeat dose as necessary. Additional supportive and resuscitative measures may be necessary while awaiting medical assistance [8][6].
Respiratory: Reversal of respiratory depression caused by partial agonists or mixed agonist/antagonists, such as buprenorphine and pentazocine, may be incomplete; dosage adjustment may be required [8].

Respiratory: Risk of pulmonary edema in postoperative patients with preexisting cardiac disease or concurrently using cardiotoxic drugs; monitoring recommended and alternative therapy may be required [8][6].
Special populations: Newborns of mothers suspected of long-term opioid use; do not administer due to risk of seizures or acute withdrawal [15]. Opioid withdrawal, which may be life-threatening if not recognized and treated, can occur in neonates; use of an alternative naloxone-containing product may be necessary, particularly during postpartum period in neonates with known or suspected exposure to maternal opioid use [8][6].
Special populations (KIDs List): Avoid in neonates for postpartum resuscitation due to risk of seizure [1]
Withdrawal: May precipitate acute withdrawal symptoms in patients with known or suspected physical dependence on opioids [8][6]; observe patients for recurrence of respiratory depression and other narcotic effects for at least 2 hours after the last dose of naloxone [15]
Withdrawal: Use in abrupt postoperative reversal of opioid depression may cause severe opioid withdrawal and has resulted in death, coma, and encephalopathy. Increased risk in patients with cardiovascular disorders or concomitant use of drugs with similar adverse cardiovascular events; monitoring recommended in patients with preexisting cardiac disease or patients who have received medications with potential adverse cardiovascular effects for hypotension, ventricular tachycardia or fibrillation, and pulmonary edema [8][6].

Adverse Effects

Abrupt reversal of opioid depression may result in nausea, vomiting, sweating, tremulousness, tachycardia, hypertension, seizures, ventricular tachycardia and fibrillation, pulmonary edema, and cardiac arrest which may result in death[5].

Nasal Spray
Common: Increased blood pressure, constipation, toothache, muscle spasms, musculoskeletal pain, headache, nasal dryness, nasal edema, nasal congestion, nasal inflammation, rhinalgia, and xeroderma [7]

Monitoring

Therapeutic Laboratory Monitoring
Reduction in opioid effects, including respiratory depression and CNS depression, is indicative of efficacy.

Toxic Physical Monitoring
Monitor for hypotension, ventricular tachycardia or fibrillation, and pulmonary edema in patients with preexisting cardiac disease or who have been treated with agents with potential for cardiovascular adverse effects [8][6].
Carefully monitor pediatric patients for signs and symptoms of relapse for at least 24 hours [8][6].
Assess administration site for residual needle parts and signs of infection in neonates and

infants under 1 year of age [6].
Monitor patients for the development of signs and symptoms of opioid withdrawal [7].
Monitor fetus for signs of distress after use in women who are pregnant [8].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action: Naloxone hydrochloride is an opioid antagonist and acts by competing for same receptor sites [10][16]. Naloxone hydrochloride reverses the effects of opioids, including respiratory depression, sedation, and hypotension. It can also reverse the psychotomimetic and dysphoric effects of agonist-antagonists such as pentazocine [7].

Pharmacodynamics
Pharmacodynamics onset, initial response
• **Opioid reversal, IV:** Within 2 minutes [7][8]
Pharmacodynamics duration, single dose
• **Opioid reversal:** Dependent on dose and route of administration [7][17]

Therapeutic Drug Concentrations
AUC
• **IM, single-dose, 0.4 mg:** 1.79 nanograms x hr/mL [7][12]
• **IM, single-dose, 5 mg:** 26.6 nanograms x hr/mL [6]
• **Intranasal, single-dose:** 4.66 to 19 nanograms x hr/mL [7][8][12]
Peak concentration
• **IM, single-dose, 0.4 mg:** 0.88 nanograms/mL [7][17]
• **IM, single-dose, 5 mg:** 17.2 ng/mL [6]
• **Intranasal, single-dose:** 2.91 to 9.7 nanograms/mL [7][12]
Time to peak concentration
• **IM:** 0.25 to 0.38 hours [7][6][17]
• **Intranasal:** 0.25 to 0.5 hours [7][8][12]

Absorption
Bioavailability
• **Intranasal:** 41.6% to 54% compared with IM [7][8][12]

Distribution
Protein binding
• **Albumin:** Relatively weak [7][17][16]

Metabolism
Sites and kinetics
• **Liver:** Extensive [7][17]
Metabolites
• **Naloxone-3-glucoronide:** major inactive [7][17]

Excretion

• **Renal excretion** 25% to 40% (within 6 hours), 50% (in 24 hours), 60% to 70% (in 72 hours) [7][17][16]

Elimination Half-Life
• **Standard syringe injection, adult:** 30 to 81 minutes [16]
• **IM, adult:** 1.24 to 1.5 hours [7][6][17]
• **Intranasal, adult:** 1.76 hours to 2.69 hours [7][8][12]
• **Neonates:** 3.1 hours [7][16]

ABOUT

Special Considerations/Preparation

Narcan® Injections
Do not mix in an alkaline solution. Available in 0.4 mg/mL (1-mL fill in 2-mL Carpuject® cartridge) and 1-mg/mL concentrations. **Store at room temperature and protect from light.**

Zimhi™ Injection Solution:
Availability: Available as a prefilled syringe with a 5 mg/0.5 mL concentration [6]
Storage: Store in outer case at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F). Do not refrigerate. Protect from light, extreme heat, and freezing. Do not reuse as each syringe contains a single dose [6].

Naloxone Nasal Spray
Storage: Store below 25 degrees C (77 degrees F); excursions permitted up to 40 degrees C (104 degrees F) [7].

Narcan® nasal spray
Availability: Blister packages containing single-dose intranasal spray cartridge (4-mg/0.1 mL dose) [10]
Storage: Store at room temperature or refrigerated at a temperature between 2 and 25 degrees C (36 and 77 degrees F). Do not freeze. Avoid excessive heat above 40 degrees C (104 degrees F). Protect from light [9]..
Product freezes at temperatures below -15 degrees C (5 degrees F) and will not spray if frozen. However, product may be thawed and may still be used if thawed after being previously frozen [10].

Kloxxado™ Nasal Spray
Availability: Blister packages containing single-dose intranasal spray cartridge (8 mg/0.1 mL) dose [8]
Storage: Store at 20 to 25 degrees C (68 to 77 degrees F); excursions permitted up to 40 degrees C (104 degrees F) and to 5 degrees C (41 degrees F). Do net freeze and protect from light [8].
Product freezes at temperatures below -15 degrees C (5 degrees F). If this happens, the

device will not spray. If frozen and needed in an emergency, do NOT wait for the product to thaw. Get emergency medical help right away. The product may be thawed by allowing it to sit at room temperature for 15 minutes, and it may still be used if it has been thawed after being previously frozen [8].

Neostigmine

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Myasthenia gravis: 0.1 mg IM (give 30 minutes before feeding).
1 mg orally (give 2 hours before feeding). Dose may have to be increased and should be titrated.

Reversal of neuromuscular blockade agent (NMBA): 0.03 to 0.07 mg/kg IV, **maximum total dose, 0.07 mg/kg**; atropine or glycopyrrolate should be administered prior to or concomitantly with neostigmine. The selection of the lower or higher dose range depends on the extent of spontaneous recovery that has occurred at the time of administration, the half-life of the NMBA being reversed, and whether there is a need to rapidly reverse the NMBA [1]. Doses of atropine 0.02 mg/kg has been used.

Uses

Neonatal transient myasthenia gravis. Neonatal persistent (congenital) myasthenia gravis.

Pediatric FDA Approved Indications
Reversal of neuromuscular blocking agents [1].

Administration

Administer IV over at least 1 minute [1]. Give with atropine or glycopyrrolate to prevent possible bradycardia, increased salivation, and hyperperistalsis [2][2][3]. For myasthenia gravis diagnosis, test dose is given IM [4][5].

MEDICATION SAFETY

Contraindications/Precautions

Contraindicated in the presence of intestinal or urinary obstruction or in the presence of peritonitis [1].

Precautions: Use cautiously in patients with bronchospasm, cardiac arrhythmia,

hypotension, or bradycardia [1][3]. Large doses may cause neuromuscular dysfunction in patients with minimal blockade; dose reduction recommended if recovery from neuromuscular blockade is nearly complete [1].

Adverse Effects

Adverse effects include muscle weakness, tremors, bradycardia, hypotension, respiratory depression, bronchospasm, diarrhea, and excessive salivation [3].

Solution Compatibility

No data.

Terminal Injection Site Compatibility

Glycopyrrolate, heparin, hydrocortisone succinate, netilmicin, pentobarbital and potassium chloride.

Monitoring

Monitor respiratory and cardiovascular status closely [3].
Train-of-four monitoring should used to evaluate recovery of neuromuscular blockade [1].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Reversible quaternary cholinesterase inhibitor which inhibits acetylcholinesterase at the neuromuscular junction, allowing accumulation of acetylcholine and thus restoring activity. In 1 study (n=27), ED50 (dose which produces 50% antagonism of neuromuscular blockade) was 13.1 mcg/kg in infants and 15.5 mcg/kg in children. Protein binding (serum albumin) of 15% to 25%. Volume of distribution of approximately 0.5 L/kg in infants and children. Undergoes hydrolysis by cholinesterase and also metabolized by microsomal enzymes in the liver to 3-hydroxy-phenyl-trimethyl ammonium. Renal excretion accounts for 50% of drug elimination. Half-life of approximately 30 to 60 minutes (shorter compared with adults) [3][6][7]. Reversal time dependent on neuromuscular blocker given and time of

administration (given at presence of intense neuromuscular blockade or delayed until recovery (first twitch recovery of 1%, 10% or 25%)) [8].

ABOUT

Special Considerations/Preparation

Prostigmin®: Available as injectable solution in 10-mL multiple dose vials in concentrations of 1 mg/mL and 0.5 mg/mL. **Protect from light**[3].
Bloxiverz™: Available as injectable solution in 10-mL multiple dose vials in concentrations of 0.5 mg/mL and 1 mg/mL. **Protect from light**[1].

Netilmicin

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Antibiotic Dosing Chart:
Renal function and drug elimination are most strongly correlated with Postmenstrual Age (PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.

Dosing Chart			
PMA (weeks)	**Postnatal (days)**	**Dose (mg/kg)**	**Interval (hours)**
≤29*	0 to 7 8 to 28 ≥29	5 4 4	48 36 24
30 to 34	0 to 7 ≥8	4.5 4	36 24
≥35	ALL	4	24
* or significant asphyxia, PDA, or treatment with indomethacin			

Uses

Treatment of infections caused by aerobic gram-negative bacilli (e.g. *Pseudomonas, Klebsiella, E coli*). Usually used in combination with a β-lactam antibiotic.

Administration

Give as an IV infusion by syringe pump over 30 minutes. Administer as a separate infusion from penicillin-containing compounds. IM injection is associated with variable absorption, especially in the very small infant.

MEDICATION SAFETY

Adverse Effects

Transient and reversible renal tubular dysfunction may occur, resulting in increased urinary losses of sodium, calcium, and magnesium. Vestibular and auditory ototoxicity. The addition of other nephrotoxic and/or ototoxic medications (e.g. furosemide, vancomycin) may increase these adverse effects. Increased neuromuscular blockade (i.e. neuromuscular weakness and respiratory failure) may occur when used with pancuronium or other neuromuscular blocking agents and in patients with hypermagnesemia.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Atropine, aztreonam, calcium gluconate, clindamycin, dexamethasone, heparin (concentrations ≤1 unit/mL), hydrocortisone succinate, iron dextran, isoproterenol, linezolid, metronidazole, norepinephrine, potassium chloride, procainamide, remifentanil, sodium bicarbonate, and vitamin K_1.

Terminal Injection Site Incompatibility

Ampicillin, furosemide, heparin (concentrations >1 unit/mL), mezlocillin, nafcillin, oxacillin, penicillin G, propofol, and ticarcillin/clavulanate.

Monitoring

Measure serum concentrations when treating for more than 48 hours. Obtain peak concentration 30 minutes after end of infusion, and trough concentration just prior to the next dose. When treating patients with serious infections or significantly changing fluid or renal status consider measuring the serum concentration 24 hours after a dose, and use the chart below for the suggested dosing interval. Blood samples obtained to monitor serum drug concentrations should be spun and refrigerated or frozen as soon as possible.

Therapeutic serum concentrations:
Peak: 5 to 12 mcg/mL (or C_{max} /MIC ratio greater than 8:1)
Trough: 0.5 to 1 mcg/mL

24- hour Concentration Suggested Dosing Intervals		
Concentration at 24 hours (mg/L)	**Half-life (hours)**	**Suggested Dosing Interval (hours)**
≤1	~ 8	24
1.1 to 2.3	~ 12	36
2.4 to 3.2	~ 15	48
≥3.3	--	Measure level in 24 hours

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Dosing recommendations are based on: (1) Higher peak concentrations increase concentration-dependent bacterial killing; (2) There is a post-antibiotic effect on bacterial killing, especially when treating concurrently with a β-lactam antibiotic; (3) There may be less toxicity with less frequent dosing, due to less renal drug accumulation. Volume of distribution is increased and clearance is decreased in patients with PDA. Serum half-life is prolonged in premature and asphyxiated newborns. Inactivation of netilmicin by penicillin-containing compounds appears to be a time-, temperature-, and concentration-dependent process. This is probably clinically significant only when penicillin-containing compounds are mixed in IV solutions or when the blood is at room temperature for several hours before the assay is performed.

ABOUT

Special Considerations/Preparation

Available in a concentration of 100 mg/mL in 1.5 mL vials. A 10 mg/mL dilution may be made by adding 1 mL of this solution to 9 mL of sterile water for injection. Dilution is stable for 72 hours refrigerated. Do not freeze. **No longer available in the US.**

Nevirapine

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Perinatal HIV Transmission, Prophylaxis:
Birth weight 1.5 to 2 kg: 8 **mg/dose** orally for 3 doses; give first dose within 48 hours of birth (start as close to time of birth as possible, preferably within 6 to 12 hours of delivery), second dose 48 hours after first dose, and third dose 96 hours after second dose. Must be administered with zidovudine. *This is the actual dose, not a mg/kg dose*[1].
Birth weight greater than 2 kg: 12 **mg/dose** orally for 3 doses; give first dose within 48 hours of birth (start as close to time of birth as possible, preferably within 6 to 12 hours of delivery), second dose 48 hours after first dose, and third dose 96 hours after second dose. Must be administered with zidovudine. *This is the actual dose, not a mg/kg dose*[1].

HIV Infection

32 to 34 weeks gestation
0 to 2 weeks: 2 mg/kg orally twice daily [2]
2 to 4 weeks: 4 mg/kg orally twice daily [2]
4 to 6 weeks: 6 mg/kg orally twice daily [2]
6 weeks or older: 200 mg/m^2 orally twice daily; option of 6 mg/kg orally twice daily for those being treated empirically [2]

34 to 37 weeks gestation
0 to 7 days of age: 4 mg/kg orally twice daily [2]
Older than 7 days : 6 mg/kg orally twice daily [2]
Older than 4 weeks: 200 mg/m^2 orally twice daily; option of 6 mg/kg orally twice daily for those being treated empirically [2]

37 weeks gestation or greater
Up to 4 weeks: 6 mg/kg orally twice daily [2].
Older than 4 weeks: 200 mg/m^2 orally twice daily; option of 6 mg/kg orally twice daily for those being treated empirically [2]

Uses

Antiretroviral Management in the Newborn: [2]

Risk of HIV in Newborn	Description	Antiretroviral (ARV) Management †

Low risk of transmission	Infants 37 weeks or older gestation when the mother: • is currently receiving or has received 10 consecutive weeks of ART during pregnancy, and • has achieved and maintained or maintained viral suppression (2 consecutive tests with HIV RNA levels less than 50 copies/mL obtained at least 4 weeks apart) for the duration of pregnancy, and • has HIV RNA <50 copies/mL at or after 36 weeks and within 4 weeks of delivery, and • did not have acute HIV infection during pregnancy, and • has reported good ART adherence, and adherence concerns have not been identified	Zidovudine for 2 weeks (footnote 1)
	•Infants born to mothers who do not meet the criteria above but who have HIV RNA <50 copies/mL at or after 36 weeks gestation	Zidovudine for 4 to 6 weeks (footnote 1)
	Premature infants (<37 weeks gestation) who are not at high risk of perinatal acquisition of HIV	

Higher risk of transmission	•Mother has not received antepartum or intrapartum ARV therapy, or •Mother has received only intrapartum ARV therapy, or •Mother has received antepartum and intrapartum ARV drugs but does not have viral suppression within 4 weeks prior to delivery, or •Mother has acute or primary HIV infection during pregnancy or breastfeeding (footnote 2)	Zidovudine, lamivudine, and nevirapine for 2 to 6 weeks; if duration of the 3-drug regimen is shorter than 6 weeks, zidovudine should be continued to complete 6 weeks of prophylaxis (footnote 3)
		Zidovudine, lamivudine, and raltegravir for 2 to 6 weeks; if duration of the 3-drug regimen is shorter than 6 weeks, zidovudine should be continued to complete 6 weeks of prophylaxis (footnote 3)
Presumed exposure	•Mother with unknown HIV status who test positive at delivery or postpartum, or whose newborn has positive HIV antibody test	•ARV management is the same as those with higher risk of transmission (see above). •Discontinue immediately if supplemental testing confirms mother does not have HIV.
Confirmed (footnote 4)	•Confirmed positive newborn HIV virologic test/nucleic acid test	Three-drug ARV regimen using treatment doses. The preferred regimen in newborns is 2 NRTIs plus nevirapine or

		raltegravir
Footnotes: 1. Zidovudine prophylaxis is recommended for infants born to mothers with HIV-2 mono-infection. If mother has HIV-1 and HIV-2 co-infection, the ARV regimen should be determined based on risk. Raltegravir should be considered in patients at high risk of perinatal HIV-2 acquisition because HIV-2 is not susceptible to nevirapine 2. Most panel members opt to administer presumptive HIV therapy to infants born to mother with acute HIV infection due to the higher risk of in utero transmission. If acute HIV is diagnosed during breastfeeding, the mother should immediately discontinue breast feeding 3. The optimal duration of presumptive HIV therapy in newborns with high risk for HIV acquisition is unknown. Patients should receive the zidovudine portion of the three-drug regimen for 6 weeks. The other two ARVs (emtricitabine/nevirapine or emtricitabine/raltegravir may be administered for 2 to 6 weeks. The recommended duration of treatment with the three-drug regimen varies depends on HIV NAT results, maternal viral load at time of delivery, and additional risk factors for HIV transmission including breastfeeding 4. ART should be initiated without waiting for results of confirmatory HIV NAT testing. However, the specimen for confirmatory testing should be attained prior to ART initiation		
Reference: https://clinicalinfo.hiv.gov /en/guidelines/pediatric-arv/whats-new April 2022		

Prevention of maternal-fetal HIV transmission: . In a phase III randomized trial (n=1684), the combination of 6 weeks of zidovudine plus 3 doses of nevirapine or the combination of 6 weeks of zidovudine plus nelfinavir and lamiVUDine for 2 weeks was associated with a lower intrapartum transmission rate when compared with zidovudine alone in infants born to women who received no antenatal antiretroviral therapy (2.2% versus 2.5% versus 4.9%, respectively). The zidovudine/nelfinavir/lamiVUDine regimen was associated with increased toxicity (eg, neutropenia) [4].

Pediatric FDA Approved Indication

Treatment of HIV-1 infection: in combination with other antiretroviral agents as either immediate release tablets or suspension in pediatric patients 15 days or older [5] or extended-release in patients 6 years or older with a body surface area of 1.17 m^2 or greater [6].

Administration

Can be given without regard to food [2].

The National Institute for Occupational Safety and Health (NIOSH) recommends the use of single gloves by anyone handling intact tablets or capsules or administering from a unit-dose package [3].
In the preparation of tablets or capsules, including cutting, crushing, or manipulating, or the handling of uncoated tablets, NIOSH recommends the use of double gloves and a protective gown. Prepare in a ventilated control device, if possible. Use respiratory protection if not prepared in a control device. During administration, wear single gloves, and wear eye/face protection if the formulation is hard to swallow or if the patient may resist, vomit, or spit up [3].
NIOSH recommends the use of double gloves and a protective gown by anyone handling a hazardous oral liquid or any hazardous drug via a feeding tube. Prepare in a control device, if possible. Use respiratory, eye, and face protection if not done in a control device. During administration, eye/face protection is needed if the patient may resist, or if there is potential to vomit or spit up [3].

MEDICATION SAFETY

Contraindications/Precautions

CONTRAINDICATIONS
Contraindicated in patients with moderate or severe hepatic impairment (Child Pugh Class B or C, respectively) [5][9].

PRECAUTIONS
Hypersensitivity reactions, including severe rash, blisters, oral lesions, conjunctivitis, facial edema, muscle or joint aches, general malaise, and significant hepatic abnormalities have been reported. The risks of hepatic events or skin reactions are greatest in the first 6 weeks of therapy. The hepatic events may occur at any time during therapy. Hepatic injury may progress despite discontinuation of treatment [5][9]. Children with CD4 percentages greater than 15% are at increased risk for hepatotoxicity and rash at initiation of nevirapine [8].
Immune reconstitution syndrome and fat redistribution may occur. Avoid concomitant use with St. John's wort-containing products, efavirenz, atazanavir, fosamprenavir (without ritonavir), boceprevir, telaprevir, or another non-nucleoside reverse transcriptase inhibitor [5][9].

Adverse Effects

Limited data on toxicity; none reported in neonates.

Common adverse events in children have been similar to those observed in adults (ie, rash, fever, nausea, headache, diarrhea, abdominal pain, fatigue, and abnormal hepatic transaminases). However, granulocytopenia was more common in children than adults [5][9]. Hepatotoxicity due to nevirapine appears to be less frequent in children than in adults [8]. In pediatric clinical studies, rash has been reported in up to 27% of patients [10][5][11]. Neutropenia (9%), anemia (7%), and hepatotoxicity (2%) have also been reported in children [9].

Black Box Warning

Severe, life-threatening, in some cases fatal, hepatotoxicity and skin reactions (eg, Stevens-Johnson syndrome; toxic epidermal necrolysis; and hypersensitivity reactions characterized by rash, constitutional findings, and organ dysfunction) have been reported. Women, including pregnant women, and/or patients with higher CD4+ cell counts are at higher risk of hepatotoxicity. Permanently discontinue nevirapine following severe hepatic, skin, or hypersensitivity reactions. Monitor patients intensively during the first 18 weeks of therapy with nevirapine to detect potentially life-threatening hepatotoxicity or skin reactions. Strictly follow the 14-day lead-in period with immediate-release nevirapine 200 mg daily dosing [5][9] .

Monitoring

Initial Neonatal Management: Obtain a baseline CBC with differential; timing of followup monitoring depends on numerous exposure risks. Recheck hemoglobin and neutrophil counts 4 weeks after initiation of prophylaxis for infants who receive combination zidovudine/lamiVUDine-containing antiretroviral prophylaxis regimens [7].
Perform virologic test at baseline, 14 to 21 days of life, 1 to 2 months of age, and 4 to 6 months of age [1].
For nevirapine, obtain ALT and AST at baseline, 2 weeks, 4 weeks, and then every 3 months [8].
Check transaminase levels immediately if a patient presents with signs or symptoms indicative of hepatitis and/or a hypersensitivity reaction, or if patient develops rash within first 18 weeks of nevirapine therapy. Permanently discontinue nevirapine in patients with rash-associated transaminase elevations [5][9].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of Action: Nevirapine is a non-nucleoside antiretroviral agent that inhibits HIV-1 replication by selectively interfering with viral reverse transcriptase without requiring intracellular metabolism. It also inactivates cell-free virions in the genital tract and breast

milk. Synergistic antiviral activity occurs when administered with zidovudine [9].

Absorption: Nevirapine is rapidly absorbed after oral administration to pregnant women [9][12].
Concentrations: The 3-dose nevirapine regimen in neonates for prevention of perinatal HIV transmission provided serum concentrations above 100 nanograms (ng)/mL in all newborns through 10 days of life [13].
All nevirapine concentrations, mostly sampled within the first 28 days of dosing, were greater than 100 ng/mL in 116 preterm infants (mean gestational age, 31.5 weeks; median birth weight, 1310 g) administered 2 mg/kg/d orally for 14 days, then 4 mg/kg/day thereafter. Median nevirapine concentrations were 4200 ng/mL before 14 days and 2300 ng/mL after 14 days (p less than 0.0001). Concentrations greater than 10,000 ng/mL were observed in 6 infants at less than 15 days of age; no adverse reactions were reported [14].
In preterm infants (28 to 37 weeks of gestation) nevirapine plasma concentrations, 8 days after birth, were greater than 100 ng/mL in 78% of infants whose mothers had received nevirapine immediately during labor and 70% in infants whose mothers had not received nevirapine during labor (p=0.49). Within 1 hour after birth, infants received a single-dose of oral nevirapine 2 mg/kg for infants less than 2 kg and 6 mg for infants greater than 2 kg [15].
Cmax: The median (range) Cmax was 1438 ng/mL (350 to 3832 ng/mL) and 1535 ng/mL (635 to 4218 ng/mL) for infants (n=58) whose mothers had received nevirapine during labor and in infants (n=23) whose mothers had not received nevirapine during labor, respectively. The preterm infants (range, 28 to 37 weeks gestation), within 1 hour after birth, received a single-dose of oral nevirapine 2 mg/kg for infants less than 2 kg and 6 mg for infants greater than 2 kg [15].
Tmax: The median (range) Tmax was 25 hours 50 minutes (9 hours 40 minutes to 83 hours 45 minutes) and 17 hours 35 minutes (7 hours 40 minutes to 29 hours) for infants (n=58) whose mothers had received nevirapine during labor and in infants (n=23) whose mothers had not received nevirapine during labor, respectively. The preterm infants (range, 28 to 37 weeks gestation), within 1 hour after birth, received a single-dose of oral nevirapine 2 mg/kg for infants less than 2 kg and 6 mg for infants greater than 2 kg [15].
AUC: The median (range) AUC was 174,134 ngXhr/mL (22,308 to 546,408) and 168,576 ngXhr/mL (20,268 to 476,712) for infants (n=58) whose mothers had received nevirapine during labor and in infants (n=23) whose mothers had not received nevirapine during labor, respectively. In small for gestational age infants (n=8), nevirapine AUC was significantly higher compared with appropriate for gestational age infants (n=15). The preterm infants (range, 28 to 37 weeks gestation), within 1 hour after birth, received a single-dose of oral nevirapine 2 mg/kg for infants less than 2 kg and 6 mg for infants greater than 2 kg [15].

Distribution: After oral administration to pregnant women, nevirapine is highly lipophilic, resulting in therapeutic concentrations being readily transferred across the placenta to the fetus [9][12].
Vd: The Vd was 1.703 L (0.624 to 6.19 L) in 23 preterm infants (24 to 37 weeks gestation) [15].

Metabolism: Nevirapine is extensively metabolized by, and an inducer of, hepatic CYP3A4 and CYP2B6 isoenzymes. Concomitant administration of phenobarbital or phenytoin (CYP3A inducers) may affect plasma concentrations [5].

Excretion

Clearance: The clearance was 34.91 mL/hr (6.2 to 163.79 ml/hr) in 23 preterm infants (24 to 37 weeks gestation). In small for gestational age infants (n=8), nevirapine clearance was significantly lower compared with appropriate for gestational age infants (n=15) after a single-dose of oral nevirapine 2 mg/kg for infants less than 2 kg and 6 mg for infants greater than 2 kg [15].

Half-life:
Serum half-life in neonates is approximately 30 to 44 hours [9][12].
Preterm Infants: The median (range) half-life was 59 hours (15.4 to 532.6 hours) and 69 hours (22.12 to 172.26 hours) for infants (n=58) whose mothers had received nevirapine during labor and in infants (n=23) whose mothers had not received nevirapine during labor, respectively [15].

ABOUT

Special Considerations/Preparation

Available: Oral suspension 10 mg/mL [16].
Storage: Store at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F); excursions permitted between 15 and 30 degrees C (59 and 86 degrees F) [16].

NiCARdipine

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Initial dose: 0.5 mcg/kg per minute continuous IV infusion.
Titrate dose to response. Blood pressure will begin to decrease within minutes of starting the infusion, reaching half of its ultimate decrease in approximately 45 minutes. Blood pressure equilibrium will not be achieved for approximately 50 hours (adult data).
Maintenance doses are usually 0.5 to 2 mcg/kg per minute.

Uses

Acute severe hypertension [4]

Nicardipine reduced blood pressure in neonatal patients experiencing hypertension while on extracorporeal membrane oxygenation (ECMO) without hypotensive episodes in a retrospective review of 8 neonates (median gestational age, 36.5 weeks; interquartile range, 35.3 to 38 weeks). The mean starting dose was 0.52 (+/- 0.22) mcg/kg/min and titrated to a maximum rate of 1.1 (+/- 0.85) mcg/kg/min (range, 0.3 to 3 mcg/kg/min) for a median duration of 51 hours (range, 4 to 227 hours) [4].

Administration

Intravenous: Dilute prior to administration to a concentration of 0.1 mg/mL or use premixed solution (0.1 mg/mL; 200 mL). Administer by a central line or large peripheral vein [1]. There are literature reports of higher concentrations being used (0.5 mg/mL) in children without significant problems, except for superficial phlebitis [2][3].

MEDICATION SAFETY

Contraindications/Precautions

Contraindications: Advanced aortic stenosis [1]

Adverse Effects

No adverse effects have been reported in neonates (small numbers). Hypotension and tachycardia are dose-dependent in adults. Headache, nausea, and vomiting were the other common effects reported.

Solution Compatibility

D_5W, NS, and D_5NS.

Solution Incompatibility

LR.

Terminal Injection Site Compatibility

Amikacin, aminophylline, aztreonam, calcium gluconate, cefazolin, ceftizoxime, chloramphenicol, cimetidine, clindamycin, dobutamine, dopamine, enalaprilat, epinephrine, erythromycin lactobionate, esmolol, famotidine, fentanyl, gentamicin, heparin (concentrations of 1 unit/mL or less), hydrocortisone, lidocaine, linezolid, lorazepam, magnesium sulfate, metronidazole, midazolam, milrinone, morphine, nafcillin, nitroglycerin, norepinephrine, penicillin G potassium, piperacillin, potassium chloride, potassium phosphate, ranitidine, sodium acetate, sodium nitroprusside, tobramycin, trimethoprim/sulfamethoxazole, vancomycin, and vecuronium.

Terminal Injection Site Incompatibility

Ampicillin, cefepime, cefoperazone, ceftazidime, furosemide, heparin (concentrations greater than 1 unit/mL), micafungin, sodium bicarbonate and thiopental.

Monitoring

Continuous monitoring of blood pressure, heart rate and rhythm during initiation of therapy, and frequently thereafter. Observe IV site for signs of irritation.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

niCARdipine is a dihydropyridine calcium channel blocker that significantly decreases systemic vascular resistance. Unlike other calcium channel blockers, it has limited effects on the myocardium. It is extensively metabolized by the liver, and is highly protein bound. Following infusion in adults, niCARdipine plasma concentrations decline tri-exponentially, with a rapid early distribution phase (alpha half-life of 2.7 minutes), an intermediate phase (beta half-life of 44.8 minutes), and a slow terminal phase (gamma half-life of 14.4 hours) that can only be detected after long-term infusions. Experience in neonates is limited, and there are no reported pharmacokinetic data.

ABOUT

Special Considerations/Preparation

Available as 2.5-mg/mL solution for injection in 10-mL ampules. **Dilute prior to administration to a concentration of 0.1 mg/mL.** Dilution is stable at room temperature for 24 hours. Also available as premixed solution (0.1 mg/mL, 0.2 mg/mL; 200 mL) in dextrose or sodium chloride. Store ampuls and premixed solution at controlled room temperature in carton until ready to use. Freezing does not adversely affect the product, but exposure to elevated temperatures should be avoided. Protect from light.

DOSING/ADMINISTRATION

Dose

Hypoxic Respiratory Failure associated with Pulmonary Hypertension
Greater than 34 weeks gestation
20 ppm. Manufacturer recommends treatment up to 14 days or until underlying oxygen desaturation has resolved and the neonate can be weaned from nitric oxide therapy. **MAX 20 ppm** [1][2][3].
If within 4 hours PaO_2 increases to at least 60 torr, decrease to 5 ppm. Continue at 5 ppm and wean fiO_2 as tolerated. When fiO_2 is less than 0.6 and ventilatory support has been decreased, wean nitric oxide in 1 ppm increments at approximately 4 hour intervals as tolerated. Discontinue when stable on 1 ppm for 4 hours. The usual length of treatment is less than 4 days. Infants who cannot be weaned off after 4 days should undergo further diagnostic testing for other diseases.

Uses

Bronchopulmonary dysplasia, prevention (premature newborn): Inhaled nitric oxide is not recommended for premature newborns for the prevention of bronchopulmonary dysplasia [5]. No differences were demonstrated in mortality, incidence of bronchopulmonary dysplasia, or respiratory or neurodevelopmental outcomes in very preterm infants (younger than 30 weeks' gestation and less than 1250 g) at 36 weeks through 24 months' postmenstrual age in a randomized trial (n=451) comparing inhaled nitric oxide and placebo initiated on postnatal days 5 to 14 and continued for 24 days [6].

Persistent pulmonary hypertension (PPHN)
Full-term newborn: Inhaled nitric oxide in term and near-term infants with PPHN or hypoxemic respiratory failure and an oxygenation index of greater than 25 reduces the need for extracorporeal membrane oxygenation. [7].
Preterm newborn: Based on the established safety profile with short and long follow-up durations [5], inhaled nitric oxide can be beneficial for preterm infants with severe hypoxemia, which is primarily due to PPHN rather than parenchymal lung disease, particularly if associated with prolonged rupture of membranes and oligohydramnios. [5][7]. A subgroup analysis of preterm infants with pulmonary hypertension did not support the use of inhaled nitric oxide during a meta-analysis of preterm infants (less than 34 weeks gestational age) on respiratory support [8].

Respiratory failure: Available evidence does not support the use in preterm infants less than 34 weeks GA [8]. This was confirmed in a multicenter, randomized, double-blind study of preterm infants born at less than 29 weeks gestation with moderate respiratory failure. Treatment was initiated within 24 hours of life with inhaled nitric oxide (5 ppm) or placebo

and continued for 7 to 21 days. The survival (without bronchopulmonary dysplasia) rate at 36 weeks postmenstrual age was 65% vs 66%, respectively. At 2 years follow-up, there was no difference in growth, neurologic development, including cerebral palsy, or respiratory outcomes between the nitric oxide group and placebo group [9]. The use of iNO in this population should be done under the auspices of a research protocol.
Low-dose inhaled nitric oxide (adjusted to 5 to 20 parts per million (ppm)) significantly reduced the use of extracorporeal membrane oxygenation (ECMO) compared with 100% nitrogen (38% vs 64%) in infants with persistent pulmonary hypertension and hypoxic respiratory failure in the randomized CINRGI trial (N=248). Overall, there was no significant difference in mortality (10 vs 13 infants), ventilator settings, heart rate, mean blood pressure, or level of dopamine support during the first 4 hours. After 1 hour of therapy, the ratio of arterial to alveolar oxygen was significantly increased in the nitric oxide group (0.1 vs 0.05). Among surviving infants, the incidence of chronic lung disease at 30 days was significantly lower in the nitric oxide group (7% vs 20%). The study gas was initiated at 20 ppm and continued for 4 hours then subsequently decreased to 5 ppm based on clinical stability within the first 24 hours, or after 24 hours of treatment in all infants [10].
In a retrospective analysis of the CINRGI study, among the 66 responders in the nitric oxide group (those who did not need ECMO), 48 patients responded within 30 minutes of therapy initiation, 6 patients within 1 hour, 8 within 24 hours, and 4 after 24 hours. Among the 48 nonresponders in the nitric oxide group (those who went on to need ECMO), 40 initially responded to therapy (22 within 30 minutes, 7 within 1 hour, 1 within 24 hours, and 10 after 24 hours) by having a 10% or more increase in PaO(2) or a 10% or greater decrease in oxygenation index, which was similar to the responding group, even though nonresponders went on to need ECMO. Of the 29 nonresponders who initially showed a response to nitric oxide therapy, PaO(2) levels at baseline were significantly lower than responders (46 vs 88 mm Hg). Among patients in the control group who responded (n=38), 20 responded within 30 minutes, 6 within 1 hour, and 11 within 24 hours, and 1 after 24 hours. Overall, disease severity at baseline did not correspond to time to improvement in oxygenation [11].

Pediatric FDA Approved Indications
Treatment of term and near-term infants (greater than 34 weeks gestation) with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension in conjunction with ventilatory support or other appropriate agents [1][3].

Administration

Genosyl®
• Administer using a calibrated Genosyl® Delivery System [1].
• Only validated ventilator systems should be used. Keep available a backup power supply to address power failures [1].
• The delivery system consists of a primary system and a fully functional second system that can be used as backup. The delivery system monitors the concentration of nitric oxide, nitrogen dioxide and air; system will shutdown if nitrogen dioxide reaches 3 parts per million (ppm) [1].
• The delivery system must be used with antioxidant cartridges not older than 12 months from the manufacturing date [1].

INOmax®
Must be administered using a calibrated FDA-cleared nitric oxide delivery system (NODS); refer to NODS labeling to determine which NODS to use. When using a NODS specifically cleared for use in the MRI suite, only use INOmax MR Conditional cylinders at 100 gauss or less [4].
Keep backup battery power supply and independent reserve nitric oxide delivery system on standby [3].

Noxivent 102™
Use equipment rated for cylinder pressure [2].

MEDICATION SAFETY

Contraindications/Precautions

Contraindications
Contraindicated in infants dependent on right-to-left cardiac blood flow [4].

Precautions
Cardiovascular: Pulmonary edema, increased pulmonary capillary wedge pressure, worsening of left ventricular dysfunction, systemic hypotension, bradycardia, and cardiac arrest may occur in patients with left ventricular dysfunction; discontinue if occurs [4]
Hematologic: Dose-related methemoglobinemia may occur and lead to hypoxemia; monitoring recommended and dosage adjustment may be necessary [4]
Respiratory: Abrupt discontinuation may worsen oxygenation and increase pulmonary artery pressure (rebound pulmonary hypertension syndrome); carefully taper dose during weaning; monitoring recommended; restart treatment immediately if rebound pulmonary hypertension occurs [4]
Respiratory: The risks of methemoglobinemia and elevated NO_2 levels increase significantly at doses greater than 20 ppm. Methemoglobin has very high affinity for oxygen and has a profound effect on oxygen content. Small increases in methemoglobin cause significant decreases in available oxygen content. Normal methemoglobin levels are less than 1%. In most neonatal studies, methemoglobinemia was defined as levels of 5% to 7%. Cyanosis develops at levels of 10%, although the patients generally remain asymptomatic. At methemoglobin levels approaching 30%, patients begin to experience respiratory distress, and cardiac, gastrointestinal, and neurologic symptoms. A methemoglobin level greater than 50% is usually lethal. Avoid concomitant use of acetaminophen, metoclopramide, sulfa drugs, topical anesthetics (EMLA, benzocaine, lidocaine, prilocaine). Congenital deficiencies in the methemoglobin reductase enzyme system occur but are rare. The environmental exposure limit set by the Occupational Safety and Health Administration is 25 ppm for NO and 5 ppm for NO_2[17].
Respiratory: Airway injury from elevated nitrogen dioxide levels may occur; monitoring recommended and dosage adjustment may be necessary [4]

Monitoring

Measure blood methemoglobin concentration 4 to 8 hours after initiation of therapy and periodically thereafter [1][12] .
Monitor inspired PaO_2 and nitrogen dioxide (NO_2) throughout administration of therapy [1][3].
Assess delivery system if there is an unexpected change in NO_2 concentration or if the NO_2 concentration reaches 0.5 ppm (Glenosyl®) [1] or 3 ppm (Inomax®) [3] when measured in the breathing circuit [1][3].
During weaning and discontinuation from therapy, monitor for hypoxemia [1][3].
Continuous monitoring of oxygenation, blood pressure and heart rate are mandatory [13][14] [15][16].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Inhaled nitric oxide (iNO) is a selective pulmonary vasodilator that decreases extrapulmonary right-to-left shunting. It activates guanylate cyclase by binding to its heme component leading to production of cyclic GMP, with subsequent relaxation of pulmonary vascular smooth muscle. Oxygenation is also improved due to the redirecting of blood from poorly aerated to better aerated distal air spaces. In addition, iNO appears to have both antioxidant and antiinflammatory activities. Systemically absorbed after inhalation. Metabolized to nitrate which is excreted in the urine [12][13].

ABOUT

Special Considerations/Preparation

INOmax®
Nitric oxide for inhalation is supplied in medical grade gas cylinders in 800 ppm concentrations. Store at room temperature [3].
Complete comprehensive periodic training program for Nitric Oxide Delivery Systems [3].
Genosyl®
Availability: Delivery system cassettes with at least 216 L of 800 ppm nitric oxide gas (at standard temperature and pressure) [1]
Storage: Store at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F) [1].

Norepinephrine

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Septic Shock
Gestational age greater than 35 weeks: Initial dose, 0.2 to 0.5 mcg/kg/min by IV infusion; titrate every 30 minutes to target blood pressure. Usual Infusion rate 0.2 to 2 mcg/kg/min; higher rates may be required [1].

Uses

Severe Sepsis and Septic Shock[3][4]

<table>
<tr><td colspan="3">Hemodynamic Support - First 60 Minutes</td></tr>
<tr><td>Time</td><td colspan="2">Management- Proceed to next step if shock persists</td></tr>
<tr><td>0 minutes</td><td colspan="2">Maintain airway and establish access</td></tr>
<tr><td>5 minutes</td><td colspan="2">Push 10 mL/kg isotonic crystalloid or colloid boluses up to 40 mL/kg until improved perfusion or unless hepatomegaly.
Begin prostaglandin infusion until rule out ductal-dependent lesion.</td></tr>
<tr><td rowspan="2">15 minutes</td><td colspan="2">DOPamine less than 10 mcg/kg/min +/- DOBUTamine for fluid-refractory shock</td></tr>
<tr><td colspan="2">EPINEPHrine 0.05 to 0.3 mcg/kg/min for fluid-refractory DOPamine-resistant shock</td></tr>
<tr><td rowspan="2">60 min</td><td>Cold shock-Poor LV function
Normal blood pressure
ScvO(2) less than 70%*/Hgb greater than 12 g/dL
SVC flow less than 40 mL/kg/min or CI less than 3.3 L/min/m(2)</td><td>Add nitrovasodilator milrinone or inamrinone with volume loading</td></tr>
<tr><td>Cold shock- Poor RV function</td><td>Inhaled nitric oxide
Inhaled iloprost or</td></tr>
</table>

	PPHN ScvO(2) less than 70%* SVC flow less than 40 mL/kg/min or CI less than 3.3 L/min/m(2)	IV adenosine IV milrinone or inamrinone
	Warm shock- Low blood pressure	Titrate volume Add norepinephrine Vasopressin or terlipressin or angiotensin
	Refractory shock	Hydrocortisone if absolute adrenal insufficiency. Triiodothyronine if hypothyroid. Begin pentoxifylline if VLBW newborn. Consider closing PDA if hemodynamically significant.
	ECMO	
Goals •First Hour: restore and maintain heart rate thresholds, capillary refill of 2 seconds or less, and normal blood pressure. • NICU: normal MAP-CVP, preductal and postductal oxygen saturation difference less than 5%, *ScvO(2) greater than 70% (except congenital heart patients with mixing lesions), SVC flow greater than 40 mL/kg/min, or cardiac index greater than 3.3 L/min/m(2)		
KEY: CI = cardiac index, Hgb = hemoglobin, LV function = left ventricle function, MAP-CVP = mean arterial pressure-central venous pressure, PDA = patent ductus arteriosus, PPHN = persistent pulmonary hypertension of the newborn, ScvO(2) = continuous central venous oxygen saturation, SVC = superior vena cava, VLBW = very low birth weight		
Davis et al: Crit Care Med 2017;45(6)		

A small observational study (n=22; gestational age greater than 35 weeks) suggested that norepinephrine be used for shock associated with hypotension and poor perfusion (cold shock) that has not responded to fluid therapy and dopamine/dobutamine. Norepinephrine was started via central venous catheter at 0.2 to 0.5 mcg/kg/min and titrated every 30 minutes to target mean blood pressure; maximum individual infusion rate was 7.1 mcg/kg/min. Mean values for systemic blood pressure (diastolic greater than systolic), heart rate, and urine output increased, while oxygen need and plasma lactate levels decreased. Three infants required extracorporeal membrane oxygenation due to persistent pulmonary

hypertension. The mortality rate was 18% [1].

Persistent pulmonary hypertension (PPHN) with circulatory failure. A small observational study (n=18; gestational age greater than 35 weeks) demonstrated that norepinephrine improved lung function in neonates with PPHN having low systemic blood pressure and reduced cardiac output despite fluid resuscitation. Norepinephrine was started via central venous catheter at 0.5 mcg/kg/min and titrated every 30 minutes to target systemic artery pressure (SAP); the maximum infusion rate was 1 mcg/kg/min. Mean SAP and mean pulmonary artery pressure (PAP) were both increased, with a concomitant decrease in the mean PAP/SAP ratio, resulting in increased pulmonary blood flow and cardiac output. In addition, median oxygen need was progressively reduced over time. No study patient required extracorporeal membrane oxygenation [5].

Administration

Administer into a large vein, check the infusion site frequently for free flow, and take care to avoid extravasation. Avoid the catheter tie-in technique [2].

Extravasation Treatment
To prevent sloughing and necrosis in areas in which extravasation has taken place, the area should be infiltrated as soon as possible using a fine hypodermic needle with saline solution containing phentolamine mesylate [2] 1 to 5 mg diluted in 5 mL of normal saline, an adrenergic blocking agent [3].

MEDICATION SAFETY

Contraindications/Precautions

Contraindications
Specific contraindications have not been determined [2].

Precautions
Administration: Extravasation may cause necrosis and sloughing of surrounding tissue. Infusion into a large vein and monitoring are recommended; treatment may be required if extravasation occurs [2].
Cardiovascular: Patients with hypovolemia as the cause of hypotension may experience severe peripheral and visceral vasoconstriction, decreased renal perfusion and reduced urine output, tissue hypoxia, lactic acidosis, and reduced systemic blood flow despite normal blood pressure; address hypovolemia before initiating therapy [2].
Cardiovascular: Mesenteric or peripheral vascular thrombosis may increase ischemia and extend area of infarction; avoid use [2].
Cardiovascular: Cardiac arrhythmias may occur, especially with hypoxia or hypercarbia; monitoring of patients with arrhythmias recommended [2]
Dermatologic: Gangrene of the extremities has occurred in patients with occlusive or

thrombotic vascular disease or with prolonged or high dose infusions; monitoring required in susceptible patients [2].
Immunologic: Allergic-type reactions, including anaphylactic symptoms and life-threatening asthmatic episodes, may occur in certain susceptible people including those with sulfite sensitivity; increased risk in asthmatic patients compared with non-asthmatic patients [2].
Withdrawal: Marked hypotension may result with sudden cessation of the infusion rate; gradual reduction of infusion rate with IV fluid administration recommended [2]

Adverse Effects

Common: Ischemic injury, bradycardia, anxiety, transient headache, respiratory difficulty, and extravasation necrosis at injection site [2].

Hypertension (6%), which resolved with dosage reduction, was noted in a report of 10 years experience with pediatric use [6]. In a report of 10 years experience with norepinephrine, 16% of patients received it by the peripheral route, without evidence of skin necrosis or distal ischemia attributed to use, for a median duration of 3 hours [6].

Solution Compatibility

D_5W, D_5NS, NS, LR

Terminal Injection Site Compatibility

Norepinephrine 0.004 mg/mL:
Famotidine 0.2 mg/mL, vasopressin 0.2 units/mL, 20 units/10 mL, and 40 units/10 mL.

Norepinephrine 0.016 mg/mL:
Propofol 10 mg/mL, vasopressin 0.2 units/mL.

Norepinephrine 0.02 mg/mL:
Clonidine 0.018 mg/mL.

Norepinephrine 0.032 mg/mL:
Dobutamine 2 mg/mL, dopamine 3.2 mg/mL, epinephrine 0.008 mg/mL.

Norepinephrine 0.064 mg/mL:
Dopamine 3.2 mg/mL, esmolol 40 mg/mL, labetalol 5 mg/mL, midazolam 1 mg/mL, milrinone 0.4 mg/mL, morphine 1 mg/mL.

Norepinephrine 0.1 mg/mL:
Dobutamine 10 mg/mL.

Norepinephrine 0.12 mg/mL:
Bivalirudin 5 mg/mL, cisatracurium 0.1, 2, and 5 mg/mL, dexmedetomidine 4 mcg/mL, diltiazem 1 mg/mL.

Norepinephrine 0.128 mg/mL:
Argatroban 1 mg/mL, caspofungin 0.5 and 0.7 mg/mL, daptomycin 10 mg/mL, diltiazem 1 mg/mL, dobutamine 4 mg/mL, dopamine 3.2 mg/mL, epinephrine 0.02 mg/mL, ertapenem 20 mg/mL, fentanyl citrate 50 mcg/mL, granisetron 50 mcg/mL, heparin 100 units/mL, hydromorphone 1 mg/mL, labetalol 2 mg/mL, linezolid 2 mg/mL, lorazepam 0.5 mg/mL, methotrexate 15 mg/mL, metronidazole 5 mg/mL, micafungin 1.5 mg/mL, midazolam 2 mg/mL, milrinone 0.2 mg/mL, morphine 2 mg/mL, mycophenolate mofetil 6 mg/mL, nicardipine 1 mg/mL, nitroglycerin 0.4 mg/mL, octreotide acetate 5 mcg/mL, ondansetron 1 mg/mL, palonosetron 50 mcg/mL, pancuronium 0.1 mg/mL, piperacillin/tazobactam 40 and 5 mg/mL, ranitidine 1 mg/mL, tacrolimus 20 mcg/mL, vecuronium 1 mg/mL, voriconazole 4 mg/mL.

Norepinephrine 0.5 mg/mL:
Amikacin 20 mg/mL, atracurium 5 mg/mL, atropine 0.5 mg/mL, aztreonam 80 mg/mL, bumetanide 0.125 mg/mL, calcium chloride 50 mg/mL, calcium gluconate 50 mg/mL, cefazolin 220 mg/mL, cefotaxime 285 mg/mL, cefotetan 400 mg/mL, cefoxitin 450 mg/mL, ceftazidime 400 mg/mL, ceftriaxone 165 mg/mL, cefuroxime 125 mg/mL, chloramphenicol 333 mg/mL, cimetidine 24 mg/mL, clindamycin 48 mg/mL, cyanocobalamin 0.5 mg/mL, cyclosporine 2 mg/mL, dexamethasone 12 mg/mL, digoxin 0.125 mg/mL, diphenhydramine 25 mg/mL, dobutamine 6.25 and 10 mg/mL, dopamine 12.8 mg/mL, doxycycline 4 mg/mL, enalaprilat 0.625 mg/mL, ephedrine 12.5 mg/mL, epinephrine 0.5 mg/mL, epoetin alfa 5000 units/mL, erythromycin 20 mg/mL, esmolol 40 mg/mL, famotidine 5 mg/mL, fentanyl 25 mcg/mL, fluconazole 2 mg/mL, gentamicin 6.4 mg/mL, glycopyrrolate 0.1 mg/mL, heparin 160 units/mL, hydrocortisone 62.5 mg/mL, imipenem/cilastatin 5 mg/mL, isoproterenol 80 mcg/mL, ketorolac 15 mg/mL, labetalol 2.5 mg/mL, lidocaine 10 mg/mL, magnesium 250 mg/mL, mannitol 150 mg/mL (15%), methyldopate 25 mg/mL, methylprednisolone 125 mg/mL, metoclopramide 2.5 mg/mL, metoprolol 0.5 mg/mL, midazolam 2.5 mg/mL, morphine 4 mg/mL, nafcillin 250 mg/mL, nalbuphine 10 mg/mL, naloxone 16 mcg/mL, netilmicin 50 mg/mL, nitroglycerin 1.6 mg/mL, ondansetron 1 mg/mL, oxacillin 160 mg/mL, papaverine 15 mg/mL, penicillin G potassium 500,000 units/mL, penicillin G sodium 500,000 units/mL, phentolamine 5 mg/mL, phenylephrine 4 mg/mL, piperacillin 320 mg/mL, potassium chloride 1 mEq/mL, procainamide 250 mg/mL, prochlorperazine 2.5 mg/mL, propranolol 0.5 mg/mL, protamine 5 mg/mL, pyridoxine 50 mg/mL, ranitidine 2 mg/mL, succinylcholine 8 mg/mL, ticarcillin/clavulanate 195 mg/mL, tobramycin 6.4 mg/mL, vancomycin 20 mg/mL, vasopressin 4 units/mL, verapamil 1.25 mg/mL.

Norepinephrine 1 mg/mL:
Argatroban 1 mg/mL, dobutamine 10 mg/mL, epinephrine 0.5 and 1 mg/mL, heparin 1 unit/mL, hydrocortisone 0.01 mg/mL, meropenem 1 and 50 mg/mL, mycophenolate mofetil 5.9 mg/mL, potassium chloride 0.04 mEq/mL, propofol 10 mg/mL.

Terminal Injection Site Incompatibility

Aminophylline, amphotericin B conventional colloidal, amphotericin B lipid complex, azathioprine, diazepam, diazoxide, foscarnet, ganciclovir, indomethacin, pentobarbital, phenobarbital, phenytoin, sodium bicarbonate, sulfamethoxazole/trimethoprim.

Monitoring

•Monitor blood pressure every 2 minutes from start of administration until target blood pressure is obtained and every 5 minutes thereafter until infusion is discontinued [2].
•Perform continuous cardiac monitoring of patients with arrhythmias [2].
•Observe for signs of extravasation. [2].
•Monitor for changes to the skin of the extremities for patients susceptible to gangrene of extremities (patients with occlusive or thrombotic vascular disease or who received prolonged or high dose infusions) [2].
•When used for septic shock, monitor hemodynamics and oxygen saturation using techniques appropriate for clinical status. Target heart rate and perfusion pressure appropriate for patient's gestational and postnatal age. For a full-term newborn, the target heart rate and perfusion pressure (mean arterial pressure minus central venous pressure) are 110 to 160 beats/min and 55 mm Hg, respectively [3].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Norepinephrine, a sympathomimetic amine, has both alpha-adrenergic activity resulting in peripheral vasoconstriction, and beta-adrenergic activity leading to inotropic stimulation of the heart and coronary artery vasodilation [2].

ABOUT

Special Considerations/Preparation

Availability: 4-mL ampules for IV infusion containing 1 mg/mL [7].
Storage: Store in the original carton at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F). Protect from light. Discard unused portion [2].
Prior to use, diluted solution may be stored for up to 24 hours at a room temperature between 20 and 25 degrees C (68 and 77 degrees F) protected from light [2].

Mix norepinephrine in dextrose solutions (dextrose 5% in water, dextrose 5% in saline) since dextrose-containing solutions protect against excessive oxidation and subsequent potency loss **Administration in saline alone is not recommended**[2]. Final concentration of 100

mcg/mL [1][5]

Nystatin

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Oral
Oral Candidiasis
Infants: 2 mL (200,000 units) orally 4 times/day; use dropper to place one-half of the dose in each side of mouth and avoid feeding for 5 to 10 minutes. Continue treatment for at least 48 hours after perioral symptoms disappear and cultures demonstrate eradication of Candida albicans [1]
Premature and low birth weight Infants: 1 mL (100,000 units) orally 4 times/day; use dropper to place one-half of the dose in each side of mouth and avoid feeding for 5 to 10 minutes. Continue treatment for at least 48 hours after perioral symptoms disappear and cultures demonstrate eradication of Candida albicans [1]

Oral
Invasive Candidiasis; Prophylaxis (birth weight less than 1500 g): 1 mL of 100,000 units/mL suspension orally 3 times per day for 6 weeks in neonatal intensive care unit (with greater than 10% rate of invasive candidiasis)[2].

Topical: Apply ointment or cream to affected area every 6 hours.
Continue treatment for 3 days after symptoms have subsided.

Uses

Treatment of mucocutaneous candidal infections. Prophylaxis against invasive fungal infections in high risk VLBW infants.

Neonatal Candidiasis[2]
Invasive candidiasis and candidemia, or very low-birth weigh infants with asymptomatic candiduria .

- Amphotericin B deoxycholate is recommended.
- Fluconazole IV or oral is an alternative for those who have not been receiving prophylaxis with fluconazole.
- Lipid formulation amphotericin B agent is an alternative; however use with caution, especially in the presence of urinary tract involvement.
- Echinocandins (caspofungin, anidulafungin, or micafungin) should be limited to salvage therapy or scenarios of resistance or toxicity to amphotericin B deoxycholate or fluconazole

Central nervous system infections

- Amphotericin B deoxycholate is recommended.
- Liposomal amphotericin B agent is an alternative.
- Salvage therapy with flucytosine may be added in those patients who have not responded to initial therapy.
- Fluconazole may be used as step-down therapy for those patients with fluconazole-susceptible isolates who respond to initial therapy

Neonatal intensive care unit (with greater than 10% rate of invasive candidiasis)

- Prophylaxis with IV or oral fluconazole for 6 weeks is recommended for neonates with birth weights of less than 1000 g
- Prophylaxis with oral nystatin is an alternative in neonates with birth weights of less than 1500 g when fluconazole is unavailable or fluconazole resistance is present

Pediatric FDA Approved Indications

Treatment of candidiasis in the oral cavity (oral suspension). Limited clinical studies in premature and low birth weight infants indicate that 1 mL four times daily is effective.[1].

Administration

•Shake well before use [1].
•Use dropper to place one-half of the dose in each side of mouth and avoid feeding for 5 to 10 minutes [1].

MEDICATION SAFETY

Adverse Effects

Possible skin rash caused by vehicle in ointment/cream.

Monitoring

Assess response to drug.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Polyene antifungal similar in structure to amphotericin B. May be fungicidal or fungistatic. Binds to the fungal cell membrane causing disruption of the cell structure. Not absorbed well from the GI tract, skin, or mucous membranes.

ABOUT

Special Considerations/Preparation

Topical ointment/cream: 100,000 units/g in 15- and 30-g tubes. Ointment dissolved in polyethylene and mineral-oil-gel base.

Topical powder: 100,000 units/g in 15- and 30-g plastic squeeze bottles.

Oral suspension: 100,000 units/mL in 60- and 473-mL bottles. Shake well before use and do not freeze. Contains less than 1% alcohol and less than 50% sucrose [1].

Octreotide

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Hyperinsulinemic hypoglycemia:
Initial dose: 1 mcg/kg/dose every 6 hours subQ or IV. Titrate upward to desired effect. Initial response should occur within 8 hours; tachyphylaxis may occur within several days.
Maximum dose: 10 mcg/kg/dose every 6 hours.

Chylothorax:
Begin at 1 mcg/kg/hour IV continuous infusion. Titrate upward as necessary based on reduction in chyle production; dosage increases of 1 mcg/kg/hour every 24 hours have been used. Infusion is decreased gradually over 2 to 7 days.
Maximum dose: 10 mcg/kg/hour.
Has also been used subQ or IV in divided doses.

Uses

Refractory hyperinsulinemic hypoglycemia:.

Congenital and postoperative chylothorax, Adjunct:.

Administration

Subcutaneous: To minimize pain, use smallest volume to deliver dose. Rotate sites [1].
Intravenous: May give IV push over 3 minutes (or rapid IV bolus in emergency situations) or by intermittent IV infusion over 15 to 30 minutes in compatible solution at a concentration of 10 to 25 mcg/mL [1][2]. May also give by continuous IV infusion. Dilutions as low as 1 mcg/mL can be used.

MEDICATION SAFETY

Adverse Effects

Vomiting, diarrhea, abdominal distention and steatorrhea may occur. Pulmonary hypertension has been reported in treated former premature infants with chronic lung disease. Necrotizing

enterocolitis has been reported in term neonates receiving octreotide for the treatment of hyperinsulinemic hypoglycemia (6 cases) and chylothorax (2 cases). Hyperglycemia may occur in patients being treated for chylothorax.

Solution Compatibility

D_5W and NS.

Terminal Injection Site Compatibility

Heparin.

Terminal Injection Site Incompatibility

Micafungin.

Monitoring

Monitor blood glucose closely. Monitor for signs and symptoms of necrotizing enterocolitis.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Octreotide is a long-acting analog of the natural hormone somatostatin. It is an even more potent inhibitor of growth hormone, glucagon, and insulin than somatostatin. Like somatostatin, it also suppresses LH response to GnRH, decreases splanchnic blood flow, and inhibits release of serotonin, gastrin, vasoactive intestinal peptide, secretin, motilin, and pancreatic polypeptide. After subcutaneous injection, octreotide is absorbed rapidly and completely from the injection site. The elimination half-life of octreotide from plasma is approximately 1.7 hours in adults compared with 1 to 3 minutes for the natural hormone. Excreted unchanged into the urine.

ABOUT

Special Considerations/Preparation

Availability: 1-mL single-dose ampules for injection containing 50-, 100-, or 500-mcg, and in 5-mL multiple-dose vials in concentrations of 200 and 1000 mcg/mL. pH 3.9 to 4.5. Osmolarity is 279 mOsm/kg.
Storage: Refrigerate and protect from light. Do not warm artificially. After initial use, multiple dose vials should be discarded within 14 days. Ampuls should be opened just prior to administration and the unused portion discarded.

For subQ injection, use undiluted drug unless dose volume is not accurately measurable. For continuous IV administration, consider making a dilution of 10 to 25 mcg/mL using D_5W or NS.

Omeprazole

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

0.5 to 1.5 mg/kg/dose orally once daily.

Uses

Crying and irritability: In otherwise healthy term infants, histamine$_2$ receptor antagonists or proton pump inhibitors should not be used for the treatment of crying and distress [1]. No improvement in crying and irritability was provided by proton pump inhibitors in infants in a systematic review of 5 randomized clinical trials (n=430) [2].

Gastroesophageal Reflux (GER): The risks associated with acid reducing agents outweighs the benefits in preterm infants for GER. Acid blocking agents should not be used and if used in preterm infants, use sparingly [3]. In otherwise healthy term infants, histamine$_2$ receptor antagonists or proton pump inhibitors should not be used for the treatment of visible regurgitation [1].
Gastroesophageal Reflux Disease (GERD): Proton pump inhibitors (PPIs) are the first-line agents for erosive esophagitis in infants and children with GERD. Histamine$_2$ receptor antagonists are the second-line agent if PPIs are not available or are contraindicated. A duration of treatment for 4 to 8 weeks for GERD symptoms is recommended. Regularly reassess the need for long-term acid suppression. If no response after 4 to 8 weeks, then re-evaluate for other causes of symptoms. H_2RAs and PPIs are not recommended for extraesophageal symptoms (e.g. cough, wheezing, asthma), unless GERD symptoms are present and/or GERD has been diagnosed [1].
A trial use of PPIs as a diagnostic test for GERD is not recommended in infants or in patients presenting with extraesophageal symptoms. However, in children with typical GERD symptoms, a trial of 4 to 8 weeks with a PPI may be used as a diagnostic test [1].

MEDICATION SAFETY

Contraindications/Precautions

CONTRAINDICATIONS
Concomitant use with rilpivirine-containing agents is **contraindicated**[7][8].

PRECAUTIONS

Concomitant use: Avoid concomitant use of clopidogrel, rifampin, and St. John's wort [9].
Dermatologic: Severe cutaneous adverse reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and acute generalized exanthematous pustulosis, have been reported with proton pump inhibitors; discontinuation required [6]
Endocrine and metabolic: Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with proton pump inhibitors for at least 3 months, with most cases after a year of therapy; serious adverse events include tetany, arrhythmias, and seizures. Monitoring recommended with prolonged treatment or with concomitant use of drugs that cause hypomagnesemia [6].
Endocrine and metabolic: Hypomagnesemia, leading to hypocalcemia and/or hypokalemia, may occur and exacerbate underlying hypocalcemia in patients with preexisting risk of hypocalcemia (eg, hypoparathyroidism); monitoring recommended, supplementation with magnesium and/or calcium, and discontinuation may be necessary [6]
Endocrine and metabolic: Cyanocobalamin (vitamin B12) deficiency may occur with long term use [10].
Immunologic: Severe cutaneous adverse reactions, including drug reaction with eosinophilia and systemic symptoms, have been reported with proton pump inhibitors; discontinuation required [6]
Immunologic: Increased risk of infections (necrotizing enterocolitis, pneumonia, upper respiratory tract infections, sepsis, urinary tract infections, and *Clostridium difficile* infections) in infants and children on H_2 blockers or PPIs demonstrated in case-control studies [1][11].
Renal: Acute tubulointerstitial nephritis has been reported and may occur at any point during therapy. May vary in presentation (symptomatic hypersensitivity reactions to non-specific symptoms of decreased renal function); discontinuation required if suspected. Diagnosis from biopsy and in the absence of extra-renal manifestations has been reported [12].
Respiratory: PPIs, when used for oropharyngeal dysphagia (off-label use), may be associated with an increased risk of hospitalization due to aspiration and isolated laryngeal penetration; demonstrated in a retrospective cohort (n=293 children 2 years or younger) [13].

Adverse Effects

Hypergastrinemia and mild transaminase elevations are the only adverse effects reported in children who received omeprazole for extended periods of time. Available data are limited to small studies of infants and children.

In a retrospective, single-center, observational, case-control study of 136 children (1 year or older) having protracted diarrhea and stool analysis for *Clostridium difficile*, the use of PPI therapy was significantly higher in the patients with *C difficile*-associated diarrhea compared to the control group (22% vs 6%; odds ratio of 4.5 (95% CI, 1.4 to 14.4; p=0.006)) [14].

Monitoring

Therapeutic Laboratory Monitoring
Consider intraesophageal pH monitoring to assess for efficacy (pH greater than 4.0) [4].

Therapeutic Physical Monitoring
Observe for symptomatic improvement within 3 days [4].

Toxic Laboratory Monitoring
Consider monitoring AST, ALT, and serum gastrin levels if duration of therapy is greater than 8 weeks (Tolia & Boyer, 2008; Gunasekaran & Hassall, 1993).
Hypomagnesemia has been reported with prolonged administration (in most cases, greater than 1 year). Monitor magnesium levels prior to initiation of therapy and periodically during therapy in patients expected to be on long-term therapy or patients receiving concomitant drugs such as digoxin or those that may cause hypomagnesemia [5]
Consider monitoring magnesium and calcium levels prior to initiating treatment and then periodically during treatment in patients with a preexisting risk of hypocalcemia (eg, hypoparathyroidism) [6]

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Omeprazole inhibits gastric acid secretion by inhibition of hydrogen-potassium ATPase, the enzyme responsible for the final step in the secretion of hydrochloric acid by the gastric parietal cell ("proton pump"). Onset of action is within one hour of administration, maximal effect is at approximately 2 hours. Inhibition of acid secretion is about 50% of maximum at 24 hours and the duration of action is approximately 72 hours.

ABOUT

Special Considerations/Preparation

Zegerid® (omeprazole/sodium bicarbonate) is supplied as a 20-mg powder for suspension packet. A 2-mg/mL concentration can be prepared by reconstituting up to a total volume of 10 mL with water. The appropriate dose can be administered through a nasogastric or orogastric tube. The suspension should be flushed through the tube with water or normal saline. Studies regarding stability of this product for partial doses have been conducted. A suspension made from six 20-mg packets mixed to a final volume of 60 mL (final concentration, 2 mg/mL) was stable under refrigeration for at least 45 days. In another study, suspensions of 0.6 to 4 mg/mL were stable under refrigeration for up to 28 days; suspensions of 1 to 4 mg/mL were stable at room temperature for 7 days, with a yellow color change.

Prilosec® is supplied as 2.5-mg and 10-mg unit dose packets for delayed-release oral

suspension (omeprazole magnesium) and as delayed-release capsules containing 10, 20, or 40-mg omeprazole as enteric-coated granules.

To prepare the delayed-release suspension, empty the 2.5 mg packet into a container containing 5 mL of water (or the 10 mg packet into a container containing 15 mL of water). Stir and leave 2 to 3 minutes to thicken. Stir and administer appropriate patient-specific dose within 30 minutes. For nasogastric or gastric tube administration, add 5 mL of water to a catheter-tipped syringe then add contents of 2.5 mg packet (or add 15 mL of water to syringe for adding 10 mg packet). Shake syringe immediately and leave 2 to 3 minutes to thicken. Shake syringe and inject patient-specific dose through the tube within 30 minutes. Flush tube with an appropriate amount of water.

Extemporaneous Suspensions: Studies regarding stability of this product for partial doses have been conducted. A suspension made from six 20-mg packets mixed to a final volume of 60 mL (final concentration, **2 mg/mL**) was stable under refrigeration for at least 45 days [15]. In another study, suspensions of **0.6 to 4 mg/mL** were stable under refrigeration for up to 28 days; suspensions of 1 to 4 mg/mL were stable at room temperature for 7 days, with a yellow color change [16].

Oseltamivir

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Influenza, Treatment
Initiate within 48 hours of influenza symptom onset[1]. *Some benefits may be apparent when initiated after 48 hours of symptom onset in patients with severe, complicated or progressive illness and in hospitalized patients* [2].
Postmenstrual age less than 38 weeks: 1 mg/kg/dose orally twice daily for 5 days. Longer treatment may be necessary for patients whose illness is prolonged, critically ill patients with respiratory failure, or immunosuppressed people [2] .
Postmenstrual age 38 to 40 weeks: 1.5 mg/kg/dose orally twice daily for 5 days. Longer treatment may be necessary for patients whose illness is prolonged, critically ill patients with respiratory failure, or immunosuppressed people [2] .
Postmenstrual age greater than 40 weeks: 3 mg/kg/dose orally twice daily for 5 days. Longer treatment may be necessary for patients whose illness is prolonged, critically ill patients with respiratory failure, or immunosuppressed people [2].
2 weeks to younger than 1 year: 3 mg/kg/dose orally twice daily for 5 days [1]. Longer treatment may be necessary for patients whose illness is prolonged, critically ill patients with respiratory failure, or immunosuppressed people [2].

Uses

Treatment of confirmed or suspected influenza virus for patients who have severe, complicated, or progressive illness, patients at higher risk of influenza complications (eg, age or underlying medical condition) or who are hospitalized. Early antiviral treatment can shorten the duration of fever and clinical illness, may reduce the risk of complications (eg, otitis media, pneumonia, respiratory) and death, and shorten the duration of hospitalization [4][5]. Those patients with severe, complicated or progressive illness and those who are hospitalized may also derive benefit even if oseltamivir is started after 48 hours of illness onset [4].
Treatment should not wait for laboratory confirmation of influenza, but instead be initiated as soon as possible after the onset of symptoms, including patients seeking medical attention more than 48 hours after onset of symptoms. The duration of therapy is 5 days [4][5], but a longer treatment duration may be considered in patients who remain severely ill after 5 days of treatment. Unless an alternative diagnosis is made, a full treatment course should be completed by patients with suspected influenza regardless of negative initial test results [4].
Oseltamivir has been used in term and preterm infants in the NICU setting for treatment and prophylaxis of influenza A virus (H1N1) with no reported safety concerns [6][7].
Neuraminidase inhibitors reduced the mortality rate (odds ratio, 0.36 (95% CI, 0.16 to 0.84), particularly if mechanical ventilation was required, in children (median age 6 years (0 to 17 years)) in the intensive care unit with laboratory-confirmed influenza in a retrospective study

(n=784). Early treatment (3 days vs 5 days) was associated with decreased mortality [8].

Administration

May be given with or without food. Food may increase tolerability in some patients [3].

MEDICATION SAFETY

Contraindications/Precautions

Precautions
Concomitant use: Concomitant use with intranasal live attenuated influenza vaccine (LAIV) not recommended within 2 weeks before or 48 hours after oseltamivir phosphate administration unless medically necessary [9]
Dermatologic: Serious skin reactions such as toxic epidermal necrolysis, Stevens-Johnson Syndrome, and erythema multiforme may occur; discontinue use if allergic-like reaction occurs [9]
Fructose intolerance: One dose delivers 2 g of sorbitol and may cause dyspepsia or diarrhea in patients with hereditary fructose intolerance [9].
Immunologic: Anaphylaxis has been reported; discontinue use if allergic-like reaction occurs [9]
Immunologic: Secondary bacterial infections may occur [9]
Psychiatric: Abnormal behavior and delirium leading to potentially fatal injuries have been reported, primarily in pediatric patients [9]
Renal: Renal impairment (ESRD not undergoing dialysis); use not recommended [9]

Adverse Effects

Most common adverse events reported in pediatric patients are nausea and vomiting [3]. Mild rash and gastrointestinal signs, and transient rise in transaminases have been reported in neonates receiving oseltamivir; no abnormal neurologic manifestations were reported.

Monitoring

Closely monitor patients with influenza for neurologic symptoms or abnormal behavior [9].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Oseltamivir phosphate, through its active form oseltamivir carboxylate, inhibits influenza virus neuraminidase which affects viral particle release. Oseltamivir exhibits activity against influenza A and influenza B viruses. Bioavailability is approximately 75%. Food has no effect on absorption. Minimal protein binding (3% for oseltamivir carboxylate). Extensively metabolized in the liver to oseltamivir carboxylate by esterases. Primarily eliminated in the kidneys (greater than 90%). Clearance is faster in younger pediatric patients compared with adults. Elimination half-life ranges from 1 to 3 hours [3]. There are very limited pharmacokinetic data in neonates or preterm infants, but it appears preterm infants would require a lower dose than term infants [10][11].

ABOUT

Special Considerations/Preparation

Available as 30-mg, 45-mg, and 75-mg capsules and oral suspension (6 mg/mL when reconstituted) [3].

Oral Suspension
In July 2011, the manufacturer changed the commercially available suspension concentration from 12 mg/mL to 6 mg/mL. There were no quality issues with the 12 mg/mL product; therefore, the 12 mg/mL suspension may remain in the marketplace and in state or national stockpiles until such supplies expire. The 12 mg/mL concentration will no longer be marketed after current supplies run out [12].
To reconstitute oral suspension, add 55 mL of water to bottle and shake well for 15 seconds. The oral suspension has a concentration of 6 mg/mL after reconstitution. Stable for 17 days refrigerated or 10 days if stored at room temperature [3].
Oseltamivir oral suspension contains 2 g of sorbitol per 75 mg dose, which exceeds the maximum daily sorbitol limit in patients with hereditary fructose intolerance, and may cause dyspepsia and diarrhea in these patients [3].

Emergency Compounding
During shortage of commercially manufactured oseltamivir (Tamiflu®) oral suspension, the suspension can be compounded using oseltamivir 75 mg capsules. The compounded suspension yields a 6 mg/mL concentration (same as commercially available 6 mg/mL suspension) and total volume adequate for 1 patient for a 5-day course of treatment or a 10-day course of prophylaxis. The compounded suspension is only to be used in emergency situations, and should not be used for convenience or when the commercially manufactured suspension is available [3].

- **Directions for Compounding**
- Determine dose and total volume required for compounding. For a dose of 15 mg or less, total volume is 37.5 mL; for 30 mg, total volume is 75 mL; for 45 mg, total volume

is 100 mL; for 60 mg, total volume is 125 mL; for 75 mg, total volume is 150 mL. If the dose is between these doses, default to the next greater dose and volume.

- Determine number of capsules, volume of water, and volume of vehicle required. Place specified amount of water into a polyethyleneterephthalate (PET) or glass bottle (2.5 mL for 3 capsules; 5 mL for 6 capsules; 7 mL for 8 capsules; 8 mL for 10 capsules; 10 mL for 12 capsules).
- Transfer contents of required number of oseltamivir 75 mg capsules into the PET or glass bottle and gently swirl for at least 2 minutes; slowly add the specified volume of vehicle (cherry syrup, Ora-Sweet(R) sugar-free, or simple syrup: 34.5 mL for 3 capsules (total volume, 37.5 mL); 69 mL for 6 capsules (total volume, 75 mL); 91 mL for 8 capsules (total volume, 100 mL); 115 mL for 10 capsules (total volume, 125 mL); 137 mL for 12 capsules (total volume, 150 mL).
- Close the bottle and shake well for 30 seconds to dissolve active drug; stable for 35 days when refrigerated (2 to 8 degrees C) or for 5 days at room temperature.

Oxacillin

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Usual dosage: 25 mg/kg/dose IV over at least 10 minutes.
Meningitis: 50 mg/kg/dose IV over at least 10 minutes.

Antibiotic Dosing Chart:
Renal function and drug elimination are most strongly correlated with Postmenstrual Age (PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.

Dosing Interval Chart		
PMA (weeks)	**PostNatal (days)**	**Interval (hours)**
≤29	0 to 28 >28	12 8
30 to 36	0 to 14 >14	12 8
37 to 44	0 to 7 >7	12 8
≥45	ALL	6

Uses

Penicillinase-producing staphylococci infections.

Infective endocarditis: The following recommendations are based on a consensus of experts [1]. The full pediatric guidelines can be found here: https://doi.org/10.1161/CIR.0000000000000298

Organism Directed Therapy		
Organism	First-Choice	Alternative Choice
Streptococci		
Highly susceptible to penicillin G (MBC 0.1 mcg/mL or less); includes most viridans streptococci,	Penicillin G or CefTRIAXone	Vancomycin or First-generation cephalosporin or CefTRIAXone

groups A, B, C, G nonenterococcal, group D streptococci (S bovis, S equinus)		
Relatively resistant to penicillin (MBC 0.2 mcg/mL or more); less-susceptible viridans streptococci or enterococci	Penicillin G or Ampicillin + Gentamicin (for first 2 weeks, or entire course for enterococci)	Vancomycin + Gentamicin for enterococci Ampicillin + CefTRIAXone (for aminoglycoside (AMG)-resistant enterococci or AMG-intolerant patient) CefTRIAXone + gentamicin (not for enterococcal endocarditis)
Resistant to penicillin	Consult an infectious disease specialist.	---
Staphylococci (S aureus or coagulase-negative staphylococci) †		
Penicillin G susceptible (1 mcg/mL or less) (rare)	Penicillin G	Oxacillin or Nafcillin or First-generation cephalosporin or Vancomycin
Penicillin G resistant (0.1 mcg/mL)	Oxacillin or Nafcillin with or without Gentamicin	Vancomycin (for those highly allergic to beta-lactam antibiotics) or First-generation cephalosporin
Oxacillin (MRSA) resistant (4 mcg/mL)	Vancomycin	Daptomycin for right-sided endocarditis, maybe for left-sided
Vancomycin resistant or intolerant	Daptomycin	Unknown

	†When prosthetic material present add riFAMpin + gentamicin (for first 2 weeks) for all staphylococci	
Gram-negative enteric bacilli	CefTAZidime or Cefepime or Cefotaxime or CefTRIAXone Plus gentamicin (or tobramycin or amikacin, depending on susceptibility)	Broad-spectrum penicillin Plus gentamicin (or tobramycin or amikacin)
HACEK group	CefTRIAXone or Cefotaxime or Ampicillin-sulbactam	Ampicillin (when susceptible) Plus aminoglycoside
KEY: AMG = aminoglycosides; HACEK = Haemophilus species, Aggregatibacter species, Cardiobacterium hominis, Eikenella corrodens, and Kingella species; MBC = minimum bactericidal concentration, MRSA = methicillin-resistant Staphylococcus aureus (includes resistance to oxacillin, nafcillin, and cephalosporins)		
Baltimore, 2015		

Administration

Intravenous: Administer IV push over 10 minutes at a **concentration not exceeding 100 mg/mL**. For intermittent IV infusion, dilute to a concentration of 10 to 40 mg/mL and infuse over 15 to 60 minutes.

MEDICATION SAFETY

Adverse Effects

Interstitial nephritis associated with hematuria, albuminuria, and casts in urine. Bone marrow depression. Elevated AST and ALT. Hypersensitivity in the form of a rash. Tolerant strains of staphylococci have been reported.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Acyclovir, cefotaxime, cefoxitin, chloramphenicol, dopamine, famotidine, fluconazole, heparin, hydrocortisone succinate, magnesium sulfate, milrinone, morphine, potassium chloride, and zidovudine.

Terminal Injection Site Incompatibility

Amikacin, caffeine citrate, gentamicin, netilmicin, sodium bicarbonate, and tobramycin.

Monitoring

Periodic CBC and urinalysis. AST, ALT. Irritating to veins--watch for phlebitis. Observe IV site for signs of extravasation.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Inhibits synthesis of bacterial cell wall. Rapidly excreted renally unchanged. Poor CSF penetration. Good penetration of pleural, pericardial, and synovial fluids.

ABOUT

Special Considerations/Preparation

Available as powder injection in 250-mg, 500-mg, 1-g, 2-g, and 10-g vials. Reconstitute 250

mg vial with 5 mL of sterile water for injection to make a concentration of 50 mg/mL. Reconstituted solution is stable for 4 days at room temperature, 7 days refrigerated. Dilute further using sterile water or NS to a concentration less than or equal to 40 mg/mL. Dilution stable for 4 days refrigerated.

Palivizumab

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Respiratory syncytial virus (RSV); prophylaxis
AAP Guidelines: *Nirsevimab is preferred to palivizumab due to its efficacy, duration and convenience*[1].
15 mg/kg per dose IM, preferably in the anterolateral aspect of the thigh [2]. Once the patient qualifies for initiation of prophylaxis, it should continue throughout the respiratory syncytial virus (RSV) season; **maximum 5 monthly doses**. Less than 5 doses is needed if born during RSV season. Discontinue if breakthrough RSV hospitalization occurs. Consider a postsurgical dose after procedures that include cardiopulmonary bypass or at the end of extracorporeal membrane oxygenation in infants younger than 24 months who are receiving prophylaxis and will continue to require prophylaxis [3][4][5].
Neonates who qualified for RSV prophylaxis may be given first dose 48 to 72 hours before hospital discharge or promptly after discharge. For most areas of the US, if prophylaxis is initiated in October, the fifth and final dose should be in February; if initiated in December, fifth and final dose should be in April. Various regions of Alaska and Florida may have different onset and end of the RSV season; RSV surveillance data generated by these States may assist with the timing of the first dose [3][4][5].

Uses

Respiratory syncytial virus (RSV); prophylaxis
AAP Recommendations:*Nirsevimab is preferred to palivizumab due to its efficacy, duration and convenience*[1]. For prophylaxis during RSV season restricted to the populations detailed below [3][4][5].
Preterm infants **without chronic lung disease (CLD) of prematurity or congenital heart disease (CHD):** May administer palivizumab in the first year of life if born before 29 weeks, 0 days gestation who are younger than 12 months at start of RSV season. NOT universally recommended if born at 29 weeks, 0 days gestation or later [3][4][5].
Palivizumab was associated with a significantly reduced rate of hospitalization for RSV (3.1% vs 5%), but the rate of hospitalization for bronchiolitis without RSV diagnosis was increased (3.3% vs 1.9%, p=0.05) in infants 29 to 32 weeks' gestation. No difference was observed for those infants 33 to 36 weeks' gestation in a retrospective study (N=14,097) [6].
Preterm infants **with CLD of prematurity:** May be considered in first year of life during RSV season in preterm infants who develop CLD of prematurity (ie, gestational age younger than 32 weeks, 0 days and require more than 21% oxygen for at least the first 28 days after birth). May be considered in the second year of life ONLY in patients with CLD of prematurity who still require medical therapy, such as chronic corticosteroids, diuretics, or supplemental oxygen, during the 6-month period before the second RSV season begins [3][4][5].
Infants **with hemodynamically significant heart disease:** May be considered in the first

year of life for infants with conditions such as acyanotic heart disease requiring medications for heart failure and anticipatory cardiac surgery as well as moderate to severe pulmonary hypertension. May also consider in children younger than 24 months who undergo cardiac transplantation during RSV season [3][4][5].
Children with **anatomic pulmonary abnormalities or neuromuscular disease:** Consider prophylaxis during first year of life if condition impairs clearance of secretions from upper airway [3][4][5].
Alaskan native populations: Due to cost associated with transportation from remote areas and burden of disease, prophylaxis may be justified [3][4][5].
Navajo and White Mountain Apache infants: Data are insufficient but prophylaxis may be justified [3][4][5].
Profoundly immunocompromised and younger than 24 months: Consider prophylaxis during RSV season [3][4][5].
Children with Down syndrome: Data are insufficient to establish efficacy for RSV infection prophylaxis [3][4][5].
Children with cystic fibrosis (CF): A single randomized controlled trial (n=186 infants; age range 0.4 to 24.4 months) did not detect any clinically meaningful differences between 5 monthly injections of palivizumab and placebo after 12 months of follow-up [7]. There was some evidence in non-randomized studies to support a role for prophylactic palivizumab in reduction of hospitalizations due to respiratory syncytial virus in a systematic review of 10 studies in 3,891 children 2 years or younger with CF; however, there was substantial inter-study variation in regimens used, risk of bias was moderate to serious, and safety and tolerability could not be ascertained [8]. Prophylaxis in children with CF is not recommended unless the child qualifies for other reasons. Consider prophylaxis if chronic lung disease is clinically evident and/or nutritional compromise is present in the first year of life. Manifestation of severe lung disease or weight less than 10th percentile may justify use through the second year [3][4][5].
Not Recommended: Infants and children with hemodynamically insignificant heart disease (eg, secundum atrial septal defect, small ventricular septal defect, pulmonic stenosis, uncomplicated aortic stenosis, mild coarctation of the aorta, and patent ductus arteriosus). Infants with lesions sufficiently revised with surgery, unless continued medication for congestive heart failure is required. Infants with mild cardiomyopathy who do not receive medical treatment for cardiomyopathy. Children in the second year of life who do not rely on medical support. For the prevention of healthcare-associated RSV disease [3][4][5].

Alternative regimen (based on mathematical modeling): Administer the second dose 29 days after the first and then subsequent doses every 38 days (total of 4 or 5 doses); initiate palivizumab on a fixed start date based on longitudinal local RSV data from previous seasons. This alternative regimen provides protection for regions that experience early and/or prolonged RSV seasons [9].

Palivizumab treatment in high-risk infants reduced the risk of RSV hospitalizations (relative risk (RR), 0.49 (95% CI, 0.37 to 0.64)) and the frequency of intensive care admissions (RR, 0.5 (95% CI, 0.3 to 0.81) by half compared with placebo in a meta-analysis (3 studies, n=2831). Economic evaluations from review of 34 additional studies ranged from highly cost-effective to not cost-effective; all studies were sponsored by pharmaceutical companies [10].

Pediatric FDA Approved Indications
Indicated for the prevention of serious lower respiratory tract disease due to respiratory syncytial virus (RSV) in pediatric patients with: [11]

- a history of premature birth (≤35 weeks gestational age) and who are 6 months of age or younger at the start of RSV season
- bronchopulmonary dysplasia that required medical treatment within the last 6 months and who are 24 months of age or younger at the start of RSV season
- hemodynamically significant congenital heart disease and who are 24 months of age or younger at the start of RSV season

Limitations of use: Not indicated for the treatment of RSV disease [11].

MEDICATION SAFETY

Contraindications/Precautions

Precautions
Anaphylaxis, anaphylactic shock, and other acute hypersensitivity reactions, some severe and/or fatal, have been reported on initial exposure or re-exposure to palivizumab; permanently discontinue if a severe hypersensitivity reaction occurs. Do not administer to patients who have had a previous significant hypersensitivity reaction to palivizumab [2].

Adverse Effects

In clinical trials, fever and rash occurred slightly more frequently in palivizumab recipients (27% and 12%, respectively) compared with those who received placebo (25% and 10%, respectively) [2].

Monitoring

Observe injection site for induration and swelling.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Synagis ® is a humanized monoclonal antibody produced by recombinant DNA technology. This composite of human (95%) and murine (5%) antibody sequences inhibits RSV replication. The mean half-life of Synagis ® is approximately 20 days. Adequate antibody titers are maintained in most infants for one month following a 15-mg/kg dose. Due to a faster metabolic rate, some hospitalized very low birth weight infants (less than 500 g) may not maintain optimal RSV titers for the entire initial month until after the second dose.

Palivizumab does not interfere with the response to other vaccines and as such, they can be administered concurrently.

ABOUT

Special Considerations/Preparation

Synagis® is supplied as 50-mg and 100-mg single-dose vials in ready-to-use, **NO RECONSTITUTION required**, liquid solution. Do not add any diluent to the liquid solution and use one dose per vial. Do not re-enter vial after initial withdrawal and discard any unused portions. Administer as soon as possible after withdrawal from the vial. **Do not FREEZE or SHAKE**.

The liquid solution should be stored **refrigerated between 2 to 8 degrees C (36 to 46 degrees F).** Synagis® contains no preservatives, thimerosal, or other mercury salts. Rubber stopper on top of vials does not contain latex [2].

Pancuronium

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Skeletal Muscle Relaxation/Paralysis:
Test dose: 0.02 mg/kg IV to measure responsiveness [1].
0.1 mg/kg (0.04 to 0.15 mg/kg) IV push, as needed for paralysis. Usual dosing interval is 1 to 2 hours. Adjust dose as needed based on duration of paralysis.

Uses

Skeletal muscle relaxation/paralysis in infants requiring mechanical ventilation. Proposed desirable effects are improved oxygenation/ ventilation, reduced barotrauma, and reduced fluctuations in cerebral blood flow.

Administration

Must be accompanied by adequate analgesia and/or sedation[1].
Administer IV push over 5 to 10 seconds. Has also been administered by continuous infusion. Concentrations are 1 to 2 mg/mL [2]. May also be diluted to 0.5 mg/mL.

MEDICATION SAFETY

Adverse Effects

Hypoxemia may occur because of inadequate mechanical ventilation and deterioration in pulmonary mechanics. Tachycardia and blood pressure changes (both hypotension and hypertension) occur frequently. Increased salivation.

Black Box Warning

According to the manufacturer's black box warning, pancuronium should be administered by adequately trained individuals familiar with its actions, characteristics, and hazards.

Solution Compatibility

D_5W, NS, and Lactated Ringer's.

Terminal Injection Site Compatibility

Aminophylline, caffeine citrate, cefazolin, cimetidine, dobutamine, dopamine, epinephrine, esmolol, fentanyl, fluconazole, gentamicin, heparin, hydrocortisone succinate, isoproterenol, lorazepam, midazolam, milrinone, morphine, nitroglycerin, nitroprusside, propofol, ranitidine, trimethoprim-sulfamethoxazole, and vancomycin.

Terminal Injection Site Incompatibility

Pentobarbital and phenobarbital.

Monitoring

Monitor vital signs frequently, blood pressure continuously. Use some form of eye lubrication.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Nondepolarizing muscle-relaxant that competitively antagonizes autonomic cholinergic receptors and also causes sympathetic stimulation. Partially hydroxylated by the liver, 40% excreted unchanged in urine. Onset of action is 1 to 2 minutes; duration varies with dose and age. Reversed by neostigmine and atropine.
Factors affecting duration of neuromuscular blockade:
Potentiation: Acidosis, hypothermia, neuromuscular disease, hepatic disease, renal failure, cardiovascular disease, younger age, aminoglycosides, hypermagnesemia, and hypokalemia.
Antagonism: Alkalosis, epinephrine, and hyperkalemia.
Sensation remains intact; analgesia should be used for painful procedures.

ABOUT

Special Considerations/Preparation

Available in concentrations of 1 mg/mL (10-mL vials) and 2 mg/mL (2-mL and 5-mL vials). Products contain 1% (10 mg/mL) benzyl alcohol. Product maintains full clinical potency for 6 months if kept at room temperature or 36 months when refrigerated. Stable for 48 hours when further diluted in compatible solution.

References

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2. Tobias JD, Lynch A, McDuffee A, et al: Pancuronium infusion for neuromuscular block in children in the pediatric intensive care unit. Anesth Analg 1995; 81(1):13-16.PubMed Abstract: http://www.ncbi.nlm.nih.gov/...

DOSING/ADMINISTRATION

Dose

2.5 mg orally every day in preterm and term neonates provided similar or slightly higher exposure compared with 40 mg orally in adults or older children in pharmacokinetic studies [1][2]. Gastric pH and the percentage of time with gastric pH above 4 were achieved, but no effect on esophageal pH, in 45 term and preterm neonates receiving 2.5 mg orally every day [3][4].

Uses

Crying and irritability: In otherwise healthy term infants, histamine$_2$ receptor antagonists or proton pump inhibitors should not be used for the treatment of crying and distress [7]. No improvement in crying and irritability was provided by proton pump inhibitors in infants in a systematic review of 5 randomized clinical trials (n=430) [8].

Gastroesophageal Reflux (GER): The risks associated with acid reducing agents outweighs the benefits in preterm infants for GER. Acid blocking agents should not be used and if used in preterm infants, use sparingly [9]. In otherwise healthy term infants, histamine$_2$ receptor antagonists or proton pump inhibitors should not be used for the treatment of visible regurgitation [7].

Gastroesophageal reflux disease (GERD): Proton pump inhibitors (PPIs) are the first-line agents for erosive esophagitis in infants and children with GERD. Histamine$_2$ receptor antagonists are the second-line agent if PPIs are not available or are contraindicated. A duration of treatment for 4 to 8 weeks for GERD symptoms is recommended. Regularly reassess the need for long-term acid suppression. If no response after 4 to 8 weeks, then re-evaluate for other causes of symptoms. H_2RAs and PPIs are not recommended for extraesophageal symptoms (e.g. cough, wheezing, asthma), unless GERD symptoms are present and/or GERD has been diagnosed [7].
A trial use of PPIs as a diagnostic test for GERD is not recommended in infants or in patients presenting with extraesophageal symptoms. However, in children with typical GERD symptoms, a trial of 4 to 8 weeks with a PPI may be used as a diagnostic test [7].
A systematic review of 5 placebo-controlled studies demonstrated a lack of effectiveness of proton pump inhibitors (lansoprazole, omeprazole, and pantoprazole) in reducing GERD symptoms in infants (34 weeks' postmenstrual age to 12 months) [10]. Pantoprazole did not improve symptoms in 129 pediatric patients 1 through 11 months of age with symptomatic GERD in a multicenter, randomized, double-blind, placebo-controlled study [3].

Stress ulcer prophylaxis: Despite the lack of data, prophylaxis with a proton pump

inhibitor or H_2RA is frequently used in pediatric [11][12] and neonatal intensive care units [11]. Prophylaxis in critically ill children admitted to the intensive care unit may be beneficial based on a systematic review of 2 studies; however the evidence was of low quality. The treatments were almagate, ranitidine, sucralfate, and omeprazole [13]. In prepubertal children with severe sepsis, experts provide no recommendation on the use of stress ulcer prophylaxis [14]. Based on low to very low quality evidence in patients older than 16 years some experts suggest acid suppression (PPIs or H_2RA) in the intensive care setting for acutely ill patients for the primary prevention of upper gastrointestinal bleeding [15].
In adults, prophylaxis (proton pump inhibitor or H_2RA) is recommended in patients with sepsis or septic shock who have risk factors for gastrointestinal bleeding. Prophylaxis should only be used in patients with risk factors [16][17].

Upper Gastrointestinal (UGI) bleeding: Acid suppression is recommended in pediatric UGI bleeds, which is supported by adult data using proton-pump inhibitors [18].

Pediatric FDA Approved Indications
Not FDA approved in neonate patients [3][5].

Administration

Oral
Delayed-Release Suspension: Mix the pantoprazole with 2.5 mL of water and immediately administer with an oral syringe. Administer 30 minutes before the first feeding at approximately the same time each day [2].

Nasogastric or Gastric Tube
Delayed-Release Suspension: Remove the plunger from the barrel of a 60-mL catheter-tip syringe. Connect the catheter tip of the syringe to a 16 French (or larger) tube. Hold the syringe attached to the tubing as high as possible while giving to prevent any bending of the tubing. Empty the contents of the packet into the barrel of the syringe and add 10 mL of apple juice; gently tap and/or shake the barrel of the syringe to help rinse the syringe and tube. Repeat at least twice more using the same amount of apple juice (10 mL) each time. No granules should remain in the syringe [3].

Intravenous: Administer as an IV infusion over 15 to 30 minutes at a concentration of 0.4 to 0.8 mg/mL [5][6] or IV push over 2 minutes at a concentration of 4 mg/mL. Flush IV line before and after administration with NS, D_5W, or LR [5].

MEDICATION SAFETY

Contraindications/Precautions

CONTRAINDICATIONS

Contraindicated [3][5]

- Known hypersensitivity to any component or any substituted benzimidazole
- Concomitant use of rilpivirine-containing products

PRECAUTIONS

Concomitant use: Elevation or and prolongation of methotrexate concentrations and/or its metabolite may occur; temporary withdrawal of proton pump inhibitor may be necessary [5].

Cardiovascular: Thrombophlebitis was associated with IV administration [5].

Dermatologic: Severe cutaneous adverse reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and acute generalized exanthematous pustulosis, have been reported with proton pump inhibitors; discontinuation required [20]

Endocrine and metabolic: Zinc supplementation may be needed in patients who are prone to zinc deficiency and receiving IV pantoprazole, which contains a chelator (edetate disodium (EDTA)). Use caution when other EDTA-containing products are co-administered IV [5].

Endocrine and metabolic: Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with proton pump inhibitors for at least 3 months, with most cases after a year of therapy; serious adverse events include tetany, arrhythmias, and seizures. Monitoring recommended with prolonged treatment or with concomitant use of drugs that cause hypomagnesemia [20].

Endocrine and metabolic: Hypomagnesemia, leading to hypocalcemia and/or hypokalemia, may occur and exacerbate underlying hypocalcemia in patients with preexisting risk of hypocalcemia (eg, hypoparathyroidism); monitoring recommended, supplementation with magnesium and/or calcium, and discontinuation may be necessary [20]

Endocrine and metabolic: Vitamin B_{12} deficiency may occur with prolonged use (e.g., longer than 3 years) [3].

Gastrointestinal: Symptomatic response does not preclude presence of gastric malignancy [3].

Gastrointestinal: Clostridioides difficile-associated diarrhea may occur, especially in hospitalized patients; use lowest dose and shortest treatment duration [21].

Hematologic: Thrombophlebitis has been reported with IV administration; monitoring required and removal of catheter recommended [21].

Hepatic: Mild, transient transaminase elevations have been observed with pantoprazole; clinical significant is unknown [5].

Immunologic: Anaphylaxis and other serious reactions such as erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported with IV pantoprazole [3]

Immunologic: New or worsening systemic or cutaneous lupus erythematosus has been reported within weeks to years of treatment initiation; avoid using for longer than medically indicated and discontinue use if suspected [3].

Immunologic: Severe cutaneous adverse reactions, including drug reaction with eosinophilia and systemic symptoms, have been reported with proton pump inhibitors; discontinuation required [20]

Infections: Increased risk of infections (necrotizing enterocolitis, pneumonia, upper respiratory tract infections, sepsis, urinary tract infections, and *Clostridium difficile* infections) in infants and children on H_2 blockers or PPIs demonstrated in case-control studies [7][22].

Lab interference: Gastric acid suppression may increase serum chromogranin A (CgA) levels; withhold pantoprazole for at least 14 days prior to neuroendocrine tumor assessment based on CgA levels [23]

Musculoskeletal: Osteoporosis-related bone fracture of hip, wrist, or spine may occur,

especially with higher (multiple daily) doses or longer duration of therapy (1 year or longer); use lowest dose and shortest treatment duration [3].
Renal: Acute tubulointerstitial nephritis has been reported and may occur at any point during therapy. May vary in presentation (symptomatic hypersensitivity reactions to non-specific symptoms of decreased renal function); discontinuation required if suspected. Diagnosis from biopsy and in the absence of extra-renal manifestations has been reported [24][25].
Respiratory: PPIs, when used for oropharyngeal dysphagia (off-label use), may be associated with an increased risk of hospitalization due to aspiration and isolated laryngeal penetration; demonstrated in a retrospective cohort (n=293 children 2 years or younger) [26].

Adverse Effects

Reported adverse effects in neonates: [4][2]

- Anemia
- Constipation
- Contact dermatitis
- Hypoxia
- Vomiting
- Rhinitis

Anemia (n=6), constipation (n=5), vomiting (n=3), hypoxia (n=5), rhinitis (n=2), and contact dermatitis (n=2) occurred in term and preterm neonates (n=61) administered pantoprazole [4][2]. One patient experienced excessive vomiting, which was probably related to pantoprazole [4].

Adverse effects reported in more than 4% of pediatric patients (1 to 16 years of age) were headache, fever, abdominal pain, vomiting, diarrhea, upper respiratory infection, and rash [3].

In a retrospective, single-center, observational, case-control study of 136 children (1 year or older) having protracted diarrhea and stool analysis for *Clostridium difficile*, the use of PPI therapy was significantly higher in the patients with *C difficile*-associated diarrhea compared to the control group (22% vs 6%; odds ratio of 4.5 (95% CI, 1.4 to 14.4; p=0.006)) [27].

Solution Compatibility

NS, D_5W, and LR.

Terminal Injection Site Compatibility

Pantoprazole diluted to concentration of 0.8 mg/mL:
Ampicillin (10 to 40 mg/mL), cefazolin (20 to 40 mg/mL), ceftriaxone (20 to 40 mg/mL), dopamine (0.8 to 3.2 mg/mL), epinephrine (16 to 32 mcg/mL), furosemide (1 to 2 mg/mL), insulin (5 to 50 units/mL), morphine (1 to 10 mg/mL), potassium chloride (20 mEq/L).

Pantoprazole diluted to concentration of 0.4 mg/mL:
Acyclovir (7 mg/mL), amikacin (5 mg/mL), aminophylline (2.5 mg/mL), amphotericin B lipid complex (1 mg/mL), amphotericin B liposome (1 mg/mL), ampicillin (10 to 40 mg/mL), ampicillin/sulbactam (20 mg/mL ampicillin), argatroban (1 mg/mL), azithromycin (2 mg/mL), bumetanide (40 mcg/mL), calcium gluconate (40 mg/mL), cefazolin (20 to 40 mg/mL), cefoxitin (20 mg/mL), ceftazidime (40 mg/mL), ceftriaxone (20 to 40 mg/mL), cefuroxime (30 mg/mL), clindamycin (10 mg/mL), digoxin (0.25 mg/mL), dopamine (0.8 to 3.2 mg/mL), enalaprilat (0.1 mg/mL), epinephrine (16 to 32 mcg/mL and 50 mcg/mL), ertapenem (20 mg/mL), fosphenytoin (20 mg PE/mL), furosemide (1 to 2 mg/mL and 3 mg/mL), ganciclovir (20 mg/mL), gentamicin (5 mg/mL), granisetron (50 mcg/mL), heparin (100 units/mL), hydrocortisone (1 mg/mL), imipenem/cilastatin (5 mg/mL imipenem), insulin (1 unit/mL and 5 to 50 units/mL), magnesium sulfate (100 mg/mL), metoclopramide (5 mg/mL), morphine (1 to 10 mg/mL), nafcillin (20 mg/mL), nitroprusside (2 mg/mL), pentobarbital (5 mg/mL), phenobarbital (5 mg/mL), phentolamine (0.2 mg/mL), piperacillin/tazobactam (40 mg/mL piperacillin), potassium chloride (20 mEq/L and 100 mEq/L), procainamide (20 mg/mL), sodium bicarbonate (1 mEq/mL), trimethoprim/sulfamethoxazole (0.8 mg/mL trimethoprim), ticarcillin/clavulanate (31 mg/mL ticarcillin), tobramycin (5 mg/mL), zidovudine (4 mg/mL).

Terminal Injection Site Incompatibility

Amphotericin B, aztreonam, calcium chloride, caspofungin, cefepime, cefotaxime, cefotetan, chloramphenicol, cimetidine, ciprofloxacin, dexamethasone, diazepam, dobutamine, dolasetron, esmolol, famotidine, fentanyl, fluconazole, hydralazine, lidocaine, linezolid, lorazepam, methylprednisolone, metronidazole, midazolam, milrinone, naloxone, nicardipine, ondansetron, pancuronium, phenytoin, propranolol, quinupristin/dalfopristin, ranitidine, rocuronium, vancomycin, vecuronium.

Monitoring

Therapeutic Laboratory Monitoring
• Consider intraesophageal pH monitoring to assess for efficacy (pH greater than 4) [19].

Toxic Laboratory Monitoring
• Hypomagnesemia has been reported with prolonged administration (in most cases, greater than 1 year). Monitor magnesium levels prior to initiation of therapy and periodically during therapy in patients expected to be on long-term therapy or patients receiving concomitant drugs such as digoxin or those that may cause hypomagnesemia [3].
• Consider monitoring magnesium and calcium levels prior to initiating treatment and then periodically during treatment in patients with a preexisting risk of hypocalcemia (eg, hypoparathyroidism) [20]

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action: Pantoprazole inhibits gastric acid secretion by inhibition of hydrogen-potassium ATPase, the enzyme responsible for the final step in the secretion of hydrochloric acid by the gastric parietal cell ("proton pump"). Antisecretory activity persists for greater than 24 hours [5].

Bioavailability: 77% [3].
AUC: 3.54 mcg X hr/mL for 1.25 mg single-oral-dose in 14 infants and 7.27 mcg X hr/mL for 2.5 mg single-oral dose in 19 infants. Infants had a corrected postmenstrual age of less than 44 weeks and a weight of 1500 g or more [2].
Protein-binding: Approximately 98% (mainly to albumin) [3].
Metabolism: Extensively metabolized in the liver by CYP2C19 and to a minor extent CYP3A4 isoenzymes [3]. Polymorphism may be displayed with the CYP2C19 isoenzyme, leading to poor metabolizers of the drug. In a pediatric (5 to 16 years of age) pharmacokinetic study, poor metabolizers (n=3) had a 6- to 14-fold increase in AUC and a 10-fold increase in half-life compared to extensive metabolizers (n=21) [28].
Excretion
Eliminated in the urine (71%) and feces (18%) [3].
Clearance: 0.21 to 0.23 L/hr/kg in 33 infants (corrected postmenstrual age of less than 44 weeks and a weight of 1500 g or more) administered a single-oral-dose of 1.25 or 2.5 mg oral pantoprazole [2]. Apparent oral clearance (L/hr/kg) was highest in the 1 to 6 years age range (1.28 to 2.08 L/hr/kg), with lower values in infants 1 to 12 months (0.87 to 1.54 L/hr/kg) [29], and children 6 years and older (0.18 to 0.41 L/hr/kg) [30].
Half-life: The mean half-lives were 3.1 hours for a 1.25 mg and 2.7 hours for the 2.5 mg oral dose in 40 infants (gestational age, 23 to 41 weeks and postnatal age, 1.3 to 19.6 weeks) [2]. Mean half-lives were approximately 1.42 to 5.34 hours and 0.7 to 0.9 hours in pediatric patients aged 1 month to 6 years [29] and 6 to 16 years, respectively [30].

ABOUT

Special Considerations/Preparation

Oral Route
Availability: 40-mg packets containing granules for delayed-release suspension and 20-mg and 40-mg delayed-release tablets [3].
Storage: Store at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F) [3].

Preparation: Make an inert powder blend with pantoprazole 2.5 mg granules. May add grape flavoring. Provided in a pouch for immediate administration after mixing with 2.5 mL of water [1][2].

Extemporaneous Oral Suspension (2 mg/mL)

Suspension is stable for 62 days under refrigeration. Shake well before using [31].

- Remove imprint from twenty 40-mg pantoprazole tablets and allow to dry
- Triturate the tablets, transfer to a beaker and add 340 mL of sterile water for irrigation, and place the beaker on a magnetic stirrer.
- Add 16.8 g of sodium bicarbonate powder and stir for about 20 minutes until the tablet remnants have disintegrated and the coating has dissolved.
- While stirring, add another 16.8 g of sodium bicarbonate powder and stir for about five minutes until the powder dissolves.
- Add enough sterile water for irrigation to bring the final volume to 400 mL and mix well

Injection Route

Availability: 40-mg freeze-dried powder in single-use vials [5].

3 Months to Less than 1 Year, 15 Minute Infusion

Reconstitute the 40-mg powder for injection vial with 10 mL of NS. Further dilute the contents of the vial with 21 mL NS to a final concentration of approximately 1.3 mg/mL. Withdraw the desired dose of the diluted pantoprazole solution and discard any unused portion. Administer IV over a period of 15 minutes [21].

Administer pantoprazole through a dedicated line or through a Y-site. Flush before and after administration with either D_5W or NS [21].

1 to 17 Years, 15 minute Infusion

Reconstitute the 40-mg powder for injection vial with 10 mL of NS. Further dilute the contents of the vial with 100 mL of NS or D5W to a final concentration of approximately 0.4 mg/mL. Withdraw the desired dose of the diluted pantoprazole solution and discard any unused portion. Administer IV over a period of 15 minutes [21].

Administer pantoprazole through a dedicated line or through a Y-site. Flush before and after administration with either D_5 W or NS n [21].

Papaverine

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

30 mg per 250 mL of arterial catheter infusion solution [1][2].

Uses

Prolongation of peripheral arterial catheter patency [1][2].

Administration

Administer a 0.12 mg/mL papaverine solution in NS or ½ NS with heparin (1 unit/mL) via intra-arterial catheter [1][2].

MEDICATION SAFETY

Adverse Effects

Use with caution in VLBW infants in the first days after birth due to potential of developing or extending an intracranial hemorrhage. Chronic hepatitis, as evidenced by an increase in serum bilirubin and serum glutamic transaminase, has been reported in three adults following long-term papaverine therapy. One patient had jaundice, and another had abnormal liver function on biopsy.

Solution Compatibility

NS, 0.45 NS, both with 1 unit/mL heparin.

Solution Incompatibility

Lactated Ringer's (precipitate forms).

Terminal Injection Site Compatibility

Phentolamine.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Papaverine directly relaxes the tonus of various smooth muscle, especially when it has been spasmodically contracted. It relaxes the smooth musculature of the larger blood vessels, especially coronary, systemic peripheral and pulmonary arteries. Vasodilation may be related to its ability to inhibit cyclic nucleotide phosphodiesterase, thus increasing levels of intracellular cyclic AMP. During administration, the muscle cell is not paralyzed and still responds to drugs and other stimuli causing contraction. Possibly because of its direct vasodilating action on cerebral blood vessels, papaverine increases cerebral blood flow and decreases cerebral vascular resistance in healthy subjects; oxygen consumption is unaltered. Papaverine is metabolized in the liver and excreted in the urine in an inactive form.

ABOUT

Special Considerations/Preparation

Supplied as 30-mg/mL solution for injection in 2-mL preservative-free vials and 10-mL multiple dose vials containing 0.5% chlorobutanol as a preservative. Vials also contain edetate disodium 0.005%.

Penicillin G benzathine

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Congenital Syphilis: 50,000 units/kg/dose IM as a single dose [1].

Dose Adjustments
Syphilis, penicillin drug shortage: During periods where aqueous crystalline penicillin G is compromised, the following is recommended (https://www.cdc.gov/std/treatment/drug-notices.htm): [1]
• For confirmed or highly probable congenital syphilis, check local sources for aqueous crystalline penicillin G (potassium or sodium) and notify the CDC and FDA of limited supply. If IV penicillin G is limited, substitute some or all daily doses with procaine penicillin G (50,000 units/kg IM daily for 10 days)
• If aqueous or procaine penicillin G is unavailable, ceftriaxone 50 to 75 mg/kg IV daily may be considered in cases with thorough clinical and serologic follow-up and in consultation with an expert due to insufficient evidence. Use caution in neonates with jaundice
• For possible or less likely congenital syphilis: (1) Procaine penicillin G 50,000 units/kg IM daily for 10 days, or (2) benzathine penicillin G 50,000 units/kg IM as a single dose
• If any part of the evaluation for congenital syphilis is abnormal, not performed, CSF examination not interpretable, or follow-up is uncertain, procaine penicillin G is recommended
• Premature neonates with no clinical evidence of congenital syphilis and might not tolerate IM injections due to muscle mass, IV ceftriaxone may be considered in cases with thorough clinical and serologic follow-up and in consultation with an expert. Dosing should be adjusted according to birthweight

Uses

Congenital syphilis: Recommended as an alternative to aqueous crystalline penicillin G or procaine penicillin G in infants who have a normal physical examination and a serum quantitative nontreponemal titer the same or less than fourfold the maternal titer and the: [1]

- mother was not treated, inadequately treated, or has no documentation of having received treatment;
- mother was treated with erythromycin or another non-penicillin regimen; OR
- mother received treatment less than 4 weeks before delivery.

Also recommended in infants whose mother was adequately treated during pregnancy (and treatment given greater than 4 weeks before delivery) and mother has no evidence of reinfection or relapse. Close serologic testing may be used instead of treatment in infants

whose mother's nontreponemal titers decreased fourfold after appropriate therapy for early syphilis and remained stable or low for late syphilis [1].
For infants whose mother's treatment was adequate before pregnancy and nontreponemal serologic titer remained low and stable before and during pregnancy and at delivery (VDRL less than 1:2; RPR less than 1:4), no treatment is required; however, it may be considered if follow-up is not assured [1].

Disease	Recommended Treatment	Alternative Treatment
Congenital Syphilis (proven or highly probable)	Aqueous Crystalline Penicillin G or Procaine Penicillin G	N/A
Congenital Syphilis (possible)	Aqueous Crystalline Penicillin G, Procaine Penicillin G, or Benzathine Penicillin G	N/A
Congenital Syphilis (less likely)	Benzathine Penicillin G	N/A
Congenital Syphilis (unlikely)	No treatment required. Serological follow up recommended in infants with reactive nontreponemal tests.	Consider benzathine penicillin G if follow up is uncertain or a reactive test occurs
Congenital Syphilis (infants and children)	Aqueous Crystalline Penicillin G	N/A
CDC Sexually Transmitted Infections Treatment Guidelines, 2021. Available at https://www.cdc.gov/std/treatment-guidelines/toc.htm		

Administration

Inspect visually for particulate matter and discoloration prior to administration. **For deep IM injection only. Do not inject into or near an artery or nerve. Do NOT inject IV or admix with other IV solutions since this has been associated with cardiorespiratory arrest and death**. Do not inject into the anterolateral thigh as quadriceps femoris fibrosis and atrophy have been reported. Administer into the upper, outer quadrant of the buttock (dorsogluteal) or the ventrogluteal site; in neonates, infants, and small children, it may be preferable to administer into the midlateral aspect of the thigh. When doses are repeated, vary the injection site. If any discoloration appears in the cartridge

upon insertion of the needle and aspiration, withdraw the needle and discard the glass TUBEX(R) cartridge. To avoid blockage of the needle, administer at a slow steady rate [2].

MEDICATION SAFETY

Contraindications/Precautions

Precautions
Administration: Inadvertent intra-arterial injection or injection near major peripheral nerves or blood vessels may lead to severe neurovascular damage, tissue cyanosis or necrosis, severe edema, or gangrene; increased risk in infants and small children; prompt management required [4].
Administration: Quadriceps femoris fibrosis and atrophy have been reported with repeated intramuscular injections in the anterolateral thigh [4].
Dermatologic: Severe cutaneous adverse reactions (SCAR), including Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, and acute generalized exanthematous pustulosis, have occurred with beta-lactam antibiotics; discontinue if suspected [3]
Gastrointestinal: Clostridium difficile-associated diarrhea, including mild diarrhea to fatal colitis, has been reported and may occur more than 2 months after use; discontinuation of antibacterial use not directed against C. difficile may be required [4].
Immunologic: Serious and occasionally fatal anaphylactic hypersensitivity reactions have been reported; increased risk in patients with a history of a severe reaction to cephalosporins or sensitivity to multiple allergens; discontinue use if reaction occurs [4].
Resistant bacterial overgrowth: Emergence and overgrowth of resistant pathogens, including fungi, may occur with prolonged therapy [4].
Special populations: Use with caution in patients with a history of asthma or significant allergies [4].

Adverse Effects

Serious and potentially fatal hypersensitivity reactions have occurred. The Jarisch-Herxheimer reaction (fever, chills, myalgia, headache, tachycardia, hyperventilation, mild hypotension) may occur after initiation of therapy in patients with syphilis. Avoid intravenous or intra-arterial administration, or injection into or near a nerve; severe neurovascular damage (transverse myelitis with permanent paralysis, gangrene requiring amputation, and necrosis and sloughing at or around injection site) has occurred, especially in infants. Quadriceps femoris fibrosis and atrophy have occurred following repeated intramuscular administration into the anterolateral thigh.

Black Box Warning

Not for intravenous use. Do not inject intravenously or admix with other intravenous solutions. There have been reports of inadvertent intravenous administration of penicillin G benzathine which has been associated with cardiorespiratory arrest and death [3].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Inhibits synthesis of bacterial cell wall. Dissolves slowly at site of injection with hydrolysis to penicillin G. Distributes widely into body tissues. Highest concentration in the kidneys, with smaller amounts in the liver, skin, and intestines. Approximately 60% bound to serum protein. Excreted rapidly by tubular excretion. In young infants and patients with renal impairment, excretion is prolonged.

ABOUT

Special Considerations/Preparation

Available in a concentration of 600,000 units/mL in 1-, 2-, and 4-mL syringes. **Store in refrigerator. Do not freeze.**

Penicillin G procaine

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Congenital Syphilis: 50,000 units/kg/dose IM once daily for 10 days [1].

Dose Adjustments
Syphilis, penicillin drug shortage: During periods where aqueous crystalline penicillin G is compromised, the following is recommended (https://www.cdc.gov/std/treatment/drug-notices.htm): [1]
• For confirmed or highly probable congenital syphilis, check local sources for aqueous crystalline penicillin G (potassium or sodium) and notify the CDC and FDA of limited supply. If IV penicillin G is limited, substitute some or all daily doses with procaine penicillin G (50,000 units/kg IM daily for 10 days)
• If aqueous or procaine penicillin G is unavailable, ceftriaxone 50 to 75 mg/kg IV daily may be considered in cases with thorough clinical and serologic follow-up and in consultation with an expert due to insufficient evidence. Use caution in neonates with jaundice
• For possible or less likely congenital syphilis: (1) Procaine penicillin G 50,000 units/kg IM daily for 10 days, or (2) benzathine penicillin G 50,000 units/kg IM as a single dose
• If any part of the evaluation for congenital syphilis is abnormal, not performed, CSF examination not interpretable, or follow-up is uncertain, procaine penicillin G is recommended
• Premature neonates with no clinical evidence of congenital syphilis and might not tolerate IM injections due to muscle mass, IV ceftriaxone may be considered in cases with thorough clinical and serologic follow-up and in consultation with an expert. Dosing should be adjusted according to birthweight

Uses

Congenital syphilis: For congenital syphilis, procaine penicillin G is recommended in neonates with proven, highly probable, or possible disease and [1]:

- an abnormal physical examination consistent with congenital syphilis;
- a serum quantitative nontreponemal serologic titer that is fourfold higher than the mother's titer; OR
- a positive darkfield test (or polymerase chain reaction) of body fluid(s) or lesions

Also recommended in neonates who have a normal physical examination and a serum quantitative nontreponemal titer the same or less than fourfold the maternal titer and the:

- mother was not treated, inadequately treated, or has no documentation of having received treatment;

- mother was treated with erythromycin or another non-penicillin G regimen; OR
- mother received treatment less than 4 weeks before delivery

Disease	Recommended Treatment	Alternative Treatment
Congenital Syphilis (proven or highly probable)	Aqueous Crystalline Penicillin G or Procaine Penicillin G	N/A
Congenital Syphilis (possible)	Aqueous Crystalline Penicillin G, Procaine Penicillin G, or Benzathine Penicillin G	N/A
Congenital Syphilis (less likely)	Benzathine Penicillin G	N/A
Congenital Syphilis (unlikely)	No treatment required. Serological follow up recommended in infants with reactive nontreponemal tests.	Consider benzathine penicillin G if follow up is uncertain or a reactive test occurs
Congenital Syphilis (infants and children)	Aqueous Crystalline Penicillin G	N/A
CDC Sexually Transmitted Infections Treatment Guidelines, 2021. Available at https://www.cdc.gov/std/treatment-guidelines/toc.htm		

Administration

For IM injection only. Avoid injection into or near an artery or nerve. Administer by deep IM injection in the midlateral aspect of the thigh. Rotate injection site for repeated administration. Needle may be blocked if injection is not made at a slow, steady rate due to high concentration of suspended material in the product.

MEDICATION SAFETY

Adverse Effects

Serious and potentially fatal hypersensitivity reactions have occurred. Avoid intravenous or intra-arterial administration, or injection into or near a nerve; severe neurovascular damage (transverse myelitis with permanent paralysis, gangrene requiring amputation, and necrosis and sloughing at or around injection site) has occurred, especially in infants. Quadriceps femoris fibrosis and atrophy have occurred following repeated intramuscular administration into the anterolateral thigh. Prolonged therapy may lead to an increased risk of neutropenia and serum sickness-like reactions.

Monitoring

Periodic monitoring of CBC and renal function is recommended.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Inhibits synthesis of bacterial cell wall. Equimolecular compound of procaine and penicillin G in a suspension. Dissolves slowly at site of injection, with maximum blood level at approximately 4 hours, declining slowly over a period of 15 to 20 hours. Distributes widely into body tissues. Highest concentration in the kidneys, with smaller amounts in the liver, skin, and intestines. Approximately 60% bound to serum protein. Excreted rapidly by tubular excretion. In young infants and patients with renal impairment, excretion is prolonged. Approximately 60% to 90% of a dose is excreted in the urine within 24 to 36 hours.

ABOUT

Special Considerations/Preparation

Available in a concentration of 600,000 units/mL in 1-, 2-, and 4-mL syringes. **Store in refrigerator. Do not freeze.**.

Penicillin G

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

»Use only aqueous crystalline penicillin G for IV administration«

Anthrax: (as part of combination or triple therapy) [1]
32 up to 34 week gestational age
0 to 1 week of age: 100,000 units/kg/dose IV every 12 hours
1 to 4 weeks of age: 100,000 units/kg/dose IV every 8 hours
34 weeks or more gestational age
0 to 1 week of age: 100,000 units/kg/dose IV every 8 hours
1 to 4 weeks of age: 100,000 units/kg/dose IV every 6 hours
Duration: 2 to 3 weeks or more until stable. Continue antimicrobial course of prophylaxis (usually oral therapy) for up to 60 days from onset of illness [1].

Congenital Syphilis: 100,000 to 150,000 units/kg/day, administered as 50,000 units/kg/dose IV over 15 minutes, given every 12 hours during the first 7 days of life, and every 8 hours thereafter for a total of 10 days [2].

Group B Streptococcal Bacteremia (Definitive Therapy) (Confirmed Early-and Late-Onset)
Preterm and Full-term
7 days and younger: 50,000 units/kg/dose IV every 12 hours for 10 days when there is no focus; may increase duration for prolonged or complicated course [3].
8 days and older: 50,000 units/kg/dose IV every 8 hours for 10 days when there is no focus; may increase duration for prolonged or complicated course [3].

Group B Streptococcal Meningitis (Definitive Therapy) (Confirmed Early-and Late-Onset)
Preterm and Full-term
7 days or younger: 150,000 units/kg/dose IV every 8 hours for 14 days for uncomplicated meningitis; may increase duration for prolonged or complicated course [3].
8 days or older: 125,000 units/kg/dose IV every 6 hours for 14 days for uncomplicated meningitis; may increase duration for prolonged or complicated course [3].

Other susceptible organisms
Bacteremia: 25,000 to 50,000 units/kg/dose IV infusion over 15 minutes, or IM.
Meningitis: 75,000 to 100,000 units/kg/dose IV infusion over 30 minutes, or IM.
Renal function and drug elimination are most strongly correlated with Postmenstrual Age (PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.

Dosing Interval Chart		
PMA	**PostNatal**	**Interval**

(weeks)	(days)	(hours)
≤29	0 to 28 >28	12 8
30 to 36	0 to 14 >14	12 8
37 to 44	0 to 7 >7	12 8
≥45	ALL	6

Dose Adjustments

Syphilis, penicillin drug shortage: During periods where aqueous crystalline penicillin G is compromised, the following is recommended (https://www.cdc.gov/std/treatment/drug-notices.htm): [2]

• For confirmed or highly probable congenital syphilis, check local sources for aqueous crystalline penicillin G (potassium or sodium) and notify the CDC and FDA of limited supply. If IV penicillin G is limited, substitute some or all daily doses with procaine penicillin G (50,000 units/kg IM daily for 10 days)

• If aqueous or procaine penicillin G is unavailable, ceftriaxone 50 to 75 mg/kg IV daily may be considered in cases with thorough clinical and serologic follow-up and in consultation with an expert due to insufficient evidence. Use caution in neonates with jaundice

• For possible or less likely congenital syphilis: (1) Procaine penicillin G 50,000 units/kg IM daily for 10 days, or (2) benzathine penicillin G 50,000 units/kg IM as a single dose

• If any part of the evaluation for congenital syphilis is abnormal, not performed, CSF examination not interpretable, or follow-up is uncertain, procaine penicillin G is recommended

• Premature neonates with no clinical evidence of congenital syphilis and might not tolerate IM injections due to muscle mass, IV ceftriaxone may be considered in cases with thorough clinical and serologic follow-up and in consultation with an expert. Dosing should be adjusted according to birthweight

Uses

Serious infections (bacteremia and meningitis) due to susceptible strains of streptococci (non enterococcal).

Congenital syphilis: For congenital syphilis, aqueous crystalline penicillin G is recommended in neonates with proven, highly probable, or possible disease and [2]:

- an abnormal physical examination consistent with congenital syphilis;
- a serum quantitative nontreponemal serologic titer that is fourfold higher than the mother's titer; OR
- a positive darkfield test (or polymerase chain reaction) of body fluid(s) or lesions

Also recommended in neonates who have a normal physical examination and a serum quantitative nontreponemal titer the same or less than fourfold the maternal titer and the:

- mother was not treated, inadequately treated, or has no documentation of having received treatment;

- mother was treated with erythromycin or another non-penicillin G regimen; OR
- mother received treatment less than 4 weeks before delivery

Disease	Recommended Treatment	Alternative Treatment
Congenital Syphilis (proven or highly probable)	Aqueous Crystalline Penicillin G or Procaine Penicillin G	N/A
Congenital Syphilis (possible)	Aqueous Crystalline Penicillin G, Procaine Penicillin G, or Benzathine Penicillin G	N/A
Congenital Syphilis (less likely)	Benzathine Penicillin G	N/A
Congenital Syphilis (unlikely)	No treatment required. Serological follow up recommended in infants with reactive nontreponemal tests.	Consider benzathine penicillin G if follow up is uncertain or a reactive test occurs
Congenital Syphilis (infants and children)	Aqueous Crystalline Penicillin G	N/A
CDC Sexually Transmitted Infections Treatment Guidelines, 2021. Available at https://www.cdc.gov/std/treatment-guidelines/toc.htm		

Group B Streptococcal (GBS) Disease
Definitive: The preferred antibiotic for early-onset and late-onset, culture confirmed-GBS disease is penicillin G and the alternative is ampicillin [3].

Infective endocarditis: The following recommendations are based on a consensus of experts [7]. The full pediatric guidelines can be found here: https://doi.org/10.1161/CIR.0000000000000298

Organism Directed Therapy		
Organism	First-Choice	Alternative Choice
Streptococci		
Highly susceptible to penicillin G (MBC 0.1 mcg/mL or less); includes	Penicillin G or CefTRIAXone	Vancomycin or First-generation cephalosporin or

most viridans streptococci, groups A, B, C, G nonenterococcal, group D streptococci (S bovis, S equinus)		CefTRIAXone
Relatively resistant to penicillin (MBC 0.2 mcg/mL or more); less-susceptible viridans streptococci or enterococci	Penicillin G or Ampicillin + Gentamicin (for first 2 weeks, or entire course for enterococci)	Vancomycin + Gentamicin for enterococci Ampicillin + CefTRIAXone (for aminoglycoside (AMG)-resistant enterococci or AMG-intolerant patient) CefTRIAXone + gentamicin (not for enterococcal endocarditis)
Resistant to penicillin	Consult an infectious disease specialist.	---
Staphylococci (S aureus or coagulase-negative staphylococci) †		
Penicillin G susceptible (1 mcg/mL or less) (rare)	Penicillin G	Oxacillin or Nafcillin or First-generation cephalosporin or Vancomycin
Penicillin G resistant (0.1 mcg/mL)	Oxacillin or Nafcillin with or without Gentamicin	Vancomycin (for those highly allergic to beta-lactam antibiotics) or First-generation cephalosporin
Oxacillin (MRSA) resistant (4 mcg/mL)	Vancomycin	Daptomycin for right-sided endocarditis, maybe for left-sided

Vancomycin resistant or intolerant	Daptomycin	Unknown
	†When prosthetic material present add riFAMpin + gentamicin (for first 2 weeks) for all staphylococci	
Gram-negative enteric bacilli	CefTAZidime or Cefepime or Cefotaxime or CefTRIAXone Plus gentamicin (or tobramycin or amikacin, depending on susceptibility)	Broad-spectrum penicillin Plus gentamicin (or tobramycin or amikacin)
HACEK group	CefTRIAXone or Cefotaxime or Ampicillin-sulbactam	Ampicillin (when susceptible) Plus aminoglycoside
KEY: AMG = aminoglycosides; HACEK = Haemophilus species, Aggregatibacter species, Cardiobacterium hominis, Eikenella corrodens, and Kingella species; MBC = minimum bactericidal concentration, MRSA = methicillin-resistant Staphylococcus aureus (includes resistance to oxacillin, nafcillin, and cephalosporins)		
Baltimore, 2015		

Anthrax[1]:

Systemic Anthrax when meningitis can be ruled out (IV)
Combination IV Therapy

- **Preferred:** Ciprofloxacin. *Alternatives in order of preference: meropenem, levofloxacin, imipenem/cilastatin, or vancomycin. If strains are penicillin-susceptible, then penicillin G (preferred) or ampicillin (alternative).*
- **Plus**
- **Preferred:** Clindamycin. *Alternatives in order of preference: linezolid, doxycycline (not for neonates 37 weeks gestation or younger), or rifampin.*

Systemic Anthrax (meningitis or disseminated infection and meningitis cannot be ruled out) (IV)
Triple IV Therapy

- **Preferred:** Ciprofloxacin. *Alternatives in order of preference: levofloxacin or*

moxifloxacin

- **Plus**
- **Preferred:** Meropenem. *Alternatives in order of preference: imipenem/cilastatin or doripenem. If strains are penicillin-susceptible, then penicillin G (preferred) or ampicillin (alternative).*
- **Plus**
- **Preferred:** Linezolid. *Alternatives in order of preference: clindamycin or rifampin or as a last resort, chloramphenicol*

Administration

Intravenous: Administer by IV intermittent infusion over 15 to 60 minutes at a concentration of 100,000 to 500,000 units/mL. Penicillin sodium contains 1.68 mEq sodium/million units and penicillin potassium contains 1.68 mEq potassium/million units and 0.3 mEq sodium/million units [4][5][6].

MEDICATION SAFETY

Adverse Effects

Cardiac arrest has been reported in patients who received high doses infused rapidly. Significant CNS toxicity has been reported in adults with renal failure who developed CSF concentrations greater than 10 mcg/mL. Bone marrow depression, granulocytopenia, and hepatitis are rare. Hypersensitivity has not been seen in neonates.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Acyclovir, amikacin, amiodarone, caffeine citrate, calcium chloride, calcium gluconate, cefotaxime, cefoxitin, chloramphenicol, cimetidine, clindamycin, dopamine, enalaprilat, erythromycin lactobionate, esmolol, fluconazole, furosemide, gentamicin, heparin, hydrocortisone succinate, lidocaine, magnesium sulfate, metronidazole, morphine, nicardipine, potassium chloride, prostaglandin E_1, ranitidine and sodium bicarbonate.

Terminal Injection Site Incompatibility

Aminophylline, amphotericin B, metoclopramide, netilmicin, pentobarbital, phenytoin, and tobramycin.

Monitoring

Follow serum sodium and potassium when using high doses and in patients with renal failure. Observe IV site for signs of extravasation.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of Action: Inhibits synthesis of bacterial cell wall.

Distribution: Distributed widely to the lung, liver, kidney, muscle, bone, and placenta. Cerebrospinal fluid penetration is poor, except in inflamed meninges [4].
Excretion: Excreted unchanged in the urine (58% to 85% of dose) [4].
Half-life: Serum half-life correlates inversely with age. In infants 14 days and older, serum half-life is approximately 1.4 hours [4].

Gestational Age	Dosage	Vd	Clearance	Half-life	Reference
28 weeks or younger	25,000 international units/kg IV every 12 hours (n=9)	0.64 L/kg (median)	0.09 L/hr/kg (median)	4.6 hours (median)	Metsvaht, 2007
	50,000 international units/kg IV every 12 hours (n=8)	0.41 L/kg (median)	0.07 L/hr/kg (median)	3.8 hours (median)	
26 to 32 weeks	50,000 international units/kg IV every 12 hours (n=20)	0.54 L (mean)	0.103 L/hr (mean)	3.9 hours (mean)	Muller, 2007

32 weeks or older	25,000 international units/kg (n=12)	0.48 L/kg (median)	0.21 L/hr/kg (median)	3.5 hours (median)	Padari, 2018
	50,000 international units/kg (n=4)	0.63 L/kg (median)	0.25 L/hr/kg (median)	4.2 hours (median)	

[8][9][10]

Gestational Age	Dosage	Median Cmin	Median Cmax (mg/L)	Median AUC(0 to 12 hours)	Reference
28 weeks or younger	25,000 international units/kg IV every 12 hours (n=9)	3.4 mg/L	58.9 mg/L	161.2 mg x hr/L	Metsvaht, 2007
	50,000 international units/kg every 12 hours (n=8)	7.1 mg/L	145.5 mg/L	389.3 mg x hr/L	
32 weeks or older	25,000 international units/kg (n=12)	3.3 mg/L	62.5 mg/L	173.6 mg x hr/L	Padari, 2018
	50,000 international units/kg (n=4)	6.4 mg/L	94.5 mg/L	225.1 mg x hr/L	

[8][9]
Penicillin G 50,000 units/kg IV every 12 hours achieved the target concentration in dose simulations of neonates 26 3/7 to 32 0/7 gestational age at 3 days of life. The target concentration was defined as the free penicillin G concentration above a MIC of 4 mg/L or less for at least 50% of the time in 100% of preterm neonates [10].

Hypothermia Penicillin G dosages of 75,000 units/kg/day IV divided every 8 hours for gestational age (GA) of 36 to 37 weeks, 150,000 units/kg/day IV divided every 8 hours for GA 38 to 41 weeks, and 200,000 units/kg/day IV divided every 6 hours for GA 42 weeks or more in neonates (younger than 6 hours) undergoing whole-body cooling for hypoxic-ischemic encephalopathy achieved target concentrations in dose simulations. The target concentration was free penicillin G concentration exceeding a MIC of 1 mg/L for at least 50% of the dosing interval for 90% or more of the simulated infants. Peak concentrations were targeted below 100 mg/L. The temperature for hypothermia was 33.5° C for 72 hours, then rewarmed 0.4° C/hr to normothermia (37° C) [11].

ABOUT

Special Considerations/Preparation

Availability: Aqueous penicillin G is available as powder for injection in two salt forms: Penicillin G potassium and penicillin G sodium. Penicillin G potassium contains 1.68 mEq (65.6 mg) potassium per 1 million units, and 0.3 mEq (6.8 mg) sodium per 1 million units. Penicillin G sodium contains 1.68 mEq (38.6 mg) sodium per 1 million units [12][13]. Penicillin G potassium is also available as a premixed frozen iso-osmotic solution containing 1, 2 or 3 million units in 50 mL [14].

Storage: Store dry powder at 20° to 25°C (68° to 77°F). Sterile constituted penicillin g *potassium* solution may be kept in refrigerator (2° to 8°C) for 7 days without significant loss of potency; sterile constituted penicillin g *sodium* solution may be kept in refrigerator (2° to 8°C) for 3 days without significant loss of potency[15][12][16][13].

Reconstitution: Note that diluent volumes for reconstitution can vary between manufacturers. Check product labeling or vial for volume to be used. Reconstitute penicillin g *potassium* vials with Water for Injection or sterile, isotonic sodium chloride injection for parenteral use [15][12][16]; reconstitute penicillin g *sodium* vials with SWFI, NS, or Dextrose Injections [13].

- **Sandoz products**

Desired Concentration (units/mL)	Diluent volume for 1,000,000 units/mL vial (mL)	Diluent volume for 5,000,000 units/mL vial (mL)	Diluent volume for infusion only (mL)
Penicillin G Potassium			
100,000	9.8	--	--
250,000	3.8	18	72
500,000	1.8	8	31.5
750,000	--	4.7	--
1,000,000	--	3	11.5
Penicillin G Sodium			
500,000	--	8	--
1,000,000	--	3	--
[12][13]			

- **Other manufacturers**

Desired Concentration (units/mL)	Diluent volume for 1,000,000 units/mL vial (mL)	Diluent volume for 5,000,000 units/mL vial (mL)	Diluent volume for infusion only (mL)
Penicillin G Potassium			
50,000	20	--	--
100,000	10	--	--
250,000	4	18.2	75

500,000	1.8	8.2	33
750,000	--	4.8	--
1,000,000	--	3.2	11.5
[15][16]			

Note: Penicillin G is also known as benzylpenicillin. Do not confuse with benzathine penicillin which is used only for IM injection. 1 million units is the equivalent of 600 mg.

PENTobarbital

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

2 to 6 mg/kg IV.

Uses

Sedative/hypnotic, for short-term use.

Administration

IV: For sedation doses, administer IV over 30 seconds to 2 minutes undiluted (50 mg/mL) [1][2][3]. May dilute to 5 mg/mL.

MEDICATION SAFETY

Adverse Effects

Respiratory depression. Tolerance, dependence, and cardiovascular depression occur with continued use. Enhances metabolism of phenytoin, sodium valproate, and corticosteroids by microsomal enzyme induction.

Black Box Warning

There are serious risks, including profound sedation, respiratory depression, coma, and/or death, associated with combined use of opioids and benzodiazepines, other drugs that depress the CNS, or alcohol. Concomitant use should be reserved for patients with no alternative treatment. If necessary, use the lowest initial dose and titrate based on clinical response. Monitor patients closely for sedation and respiratory depression. Screen patients for risk of substance-use disorders [4].

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Acyclovir, amikacin, aminophylline, atropine, calcium chloride, chloramphenicol, erythromycin lactobionate, hyaluronidase, insulin, lidocaine, linezolid, neostigmine, and propofol.

Terminal Injection Site Incompatibility

Fat emulsion. Cimetidine, fentanyl, hydrocortisone succinate, midazolam, morphine, pancuronium bromide, penicillin G, phenytoin, ranitidine, and vancomycin. No data are currently available on heparin and potassium chloride.

Monitoring

Monitor respiratory status and blood pressure closely.
Serum concentration for sedation: 0.5 to 3 mcg/mL.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Short-acting barbiturate. PENTobarbital has no analgesic effects. Serum half-life is dose-dependent (15 to 50 hours in adults) and unknown in neonates. Metabolized by hepatic microsomal enzyme system.

ABOUT

Special Considerations/Preparation

Injection
Available: 50-mg/mL solution in 20 mL and 50 mL multidose vials. Solution contains propylene glycol 40%, and alcohol 10%. Irritating to veins; pH is 9.5.

A 5-mg/mL dilution may be made by adding 1 mL of the 50-mg/mL solution to 9 mL of preservative-free normal saline. Use immediately.
Stability: At least 95% of the initial concentration of PENTobarbital remained on day 100 when PENTobarbital 50 mg/mL was stored at room temperature in polypropylene syringes [5].

DOSING/ADMINISTRATION

Dose

Anticonvulsant:
Loading dose: 20 mg/kg IV [1][2][3].
Second loading dose
Preterm infants, preservative-free formulation: Give an additional 10 mg/kg or 20 mg/kg IV if seizures persist or recur any time 15 minutes after completion of the initial loading dose (FDA dosage) [1]
Term infants, preservative-free formulation: Give and additional 20 mg/kg IV if seizures persist or recur any time 15 minutes after completion of the initial loading dose (FDA dosage) [1]
Give additional doses of 10 mg/kg/dose as required every 20 to 30 minutes up to a total dose of 40 mg/kg (guideline dosage) [2].
Maintenance:
Preservative-free formulation, FDA dosage: 1.5 mg/kg IV every 8 hours **OR** 2.25 mg/kg IV every 12 hours **MAX 4.5 mg/kg/day for up to 5 days**[1]
Guideline dosage: 3 to 5 mg/kg/day IV in 1 to 2 divided doses started 12 hours after the loading dose [2].
PHENobarbital can also be administered orally or intramuscularly [4][5].
Very low birth weight (less than 1500 g), preterm infants, may require lower loading doses of less than 15 mg/kg IV followed by single injection of less than 3 mg/kg/day 24 hours later [6].

Neonatal Abstinence Syndrome:
Loading dose: 16 mg/kg orally on day 1 [7][8][9].
Maintenance: 1 to 4 mg/kg/dose orally every 12 hours [7][8][9].
Based on abstinence scoring, weaning can be achieved by decreasing dose 20% every other day.

Dose Adjustments
Concomitant use (QTc prolonging agents/agents that increase phenobarbital concentration): Avoid use [1]
Drug reaction with eosinophilia and systemic symptoms (DRESS): Discontinue if an alternative etiology for signs and symptoms cannot be established [1]
Extracorporeal Membrane Oxygenation (ECMO) in neonates (median, 3.5 kg, 49 cm) and infants (median 8 kg, 77 cm) receiving phenobarbital for seizures, sedation, and withdrawal symptoms undergoing ECMO: Median loading dose, 15 mg/kg (95% CI, 9.9 to 19.8 mg/kg) IV over 15 minutes; median maintenance dosage, 4 mg/kg/day (95% CI, 3.5 to 5.4 mg/kg/day) IV over 15 minutes divided in 2 or 3 doses every 8 to 12 hours to achieve a target therapeutic range of 10 to 40 mg/L [10].
Hypersensitivity reactions: Evaluate patient immediately; discontinue therapy if an alternative etiology for the signs and symptoms cannot be established [1]
Infusion reactions: Stop injection for any evidence of pain, swelling, discoloration, or

temperature change in the limb [1]
Rash: Discontinue at the first sign of a rash, unless the rash is clearly not drug-related [1]
Stevens-Johnson syndrome/Toxic epidermal necrolysis (SJS/TEN): Discontinue and do not resume; alternative therapy should be considered [1]

Uses

Anticonvulsant: PHENobarbital is the first-line agent for neonatal seizures. The second-line agents, when seizures are not controlled with the maximal tolerated dose of PHENobarbital, are a benzodiazepine, phenytoin, levETIRAcetam, or lidocaine [14][2][15]. PHENobarbital reduced electrographic seizure burden within 1 hour of administration and for a duration of up to 4 hours (n=19) [3].
PHENobarbital vs levETIRAcetam: The rate of achieving and maintaining electrographic seizure freedom for 24 hours in neonates was significantly higher in patients taking PHENobarbital compared with levETIRAcetam (80% vs 28%, respectively; RR 0.35, 95% CI 0.22 to 0.56) in a prospective study (N=83). The seizure-free rates at 1-hour (93% vs 49%), 48-hours (64% vs 17%), and in patients with hypoxic-ischemic encephalopathy (90% vs 35%) were also significantly lower in the PHENobarbital group. Grade 4 serious adverse effects reported included hypotension (n=5) and respiratory depression (n=1). Patients were randomized to receive loading doses of PHENobarbital 20 mg/kg or levETIRAcetam 40 mg/kg. An additional 20 mg/kg dose was given for both drugs if required 30 minutes after the start of the first dose [16].

Cholestasis: During first course therapy, ursodiol reduced direct bilirubin by 1.89 mg/dL compared with an increase of 0.76 mg/dL (p = 0.03) for PHENobarbital in a retrospective study of 68 preterm and term newborns with direct bilirubin greater than 3 mg/dL. The change for all treatment courses were -3.96 mg/dL for ursodiol and +0.28 mg/dL for PHENobarbital. Median dosages were ursodiol 27.43 mg/kg/day enterally and PHENobarbital 4.48 mg/kg/day IV [17].
Neonates and infants in the NICU with a direct bilirubin of 2 mg/dL or greater had significantly increased direct bilirubin levelswith PHENobarbital compared with the control group in a retrospective study (N=52). During the 8 study weeks, the percent change of direct bilirubin in the PHENorbarbital group during each week ranged from an 8% to 37.8% increase from the mean baseline of 4.7 mg/dL and ended on week 8 with a 11.2% increase in direct bilirubin. The percent change of direct bilirubin in the control group during each week ranged from a 0.7% to 48.5% decrease from the mean baseline of 4.7 mg/dL and ended on week 8 with a 48.5% decrease in direct bilirubin. Low body weight and gastrointestinal obstruction had a significant effect on direct bilirubin concentrations, resulting in lesser improvements of direct bilirubin. Mean PHENObarbital dose was 5 mg/kg/day [18].

Neonatal abstinence syndrome (NAS) in nonopiate- or polydrug-exposed infants [7][8][9]. In a prospective, randomized, open-label trial, infants 35 weeks gestational age or older treated with morphine for NAS experienced shorter morphine treatment days (4.6 less days (95% CI, 0.3 to 8.9 days)) and no difference in morphine total dose with adjunctive PHENobarbital compared with cloNIDine. However, the total duration of PHENobarbital therapy continued for an average of 3.8 months (range 1 to 8 months) [19].

Sublingual buprenorphine was associated with the largest reduction in length of treatment and length of stay for NAS in a network meta-analysis of 18 randomized controlled trials (n=1072) of buprenorphine, clonidine, diluted tincture of opium and clonidine, diluted tincture of opium, morphine, methadone, and phenobarbital. Morphine was the least effective opioid [20]. The findings should be interpreted with caution due to significant study limitations [20][21]

May enhance bile excretion in patients with cholestasis before ^{99}Tc-IDA scanning.

FDA Approved Pediatric Indications
Indicated for the treatment of neonatal seizures in term and preterm infants [1]

Administration

Intravenous
- Administer IV over 15 [1][11] to 30 minutes [11]
- Administer into a large peripheral vein [1]
- Final concentration is 10 mg/mL [1] or 65 mg/mL (guideline dosage) [11].
- PHENobarbital sodium can be diluted to 10 mg/mL in normal saline prior to administration [1][12] using 10 mL of 0.9% sodium chloride [1]l.

Oral: The intravenous formulation of PHENobarbital, diluted to 10 mg/mL, has been used orally. An extemporaneous PHENobarbital suspension can also be used to avoid alcohol content in the PHENobarbital oral and IV solution (See Special Considerations/Preparation) [13].

MEDICATION SAFETY

Contraindications/Precautions

Contraindicated
- Acute porphyria (IV powder for solution) [1]
- History of manifest or latent porphyria [22]
- Intraarterial administration; adverse reactions ranging from transient pain to gangrene may occur [22]
- History of addiction to sedative-hypnotic medications; normal doses may be ineffective and contribute to further addiction [22]
- Large doses in patients with nephritic syndrome [22]
- Marked hepatic impairment [22]
- Severe respiratory distress with dyspnea or obstruction [22]
- Subcutaneous administration; tissue irritation ranging from tenderness and redness to necrosis may occur [22]

Precautions

Addiction potential: Tolerance and psychological and physical dependence may occur; use with caution in patients with mental depression, suicidal tendencies, and history of drug abuse [22].
Administration: Use not recommended in neonates (children less than 1 month of age) due to presence of benzyl alcohol; fatal gasping syndrome has been reported [22].
Administration: Severe respiratory depression, apnea, hypertension, laryngospasm, or vasodilation with fall in blood pressure may occur with rapid IV administration; peak concentrations in the brain may take 15 minutes or more following administration [22].
Administration: Avoid extravascular injection; necrosis may occur [23]
Cardiovascular: Use with extreme caution in patients with cardiac disease, shock, or great debility [22].
Cardiovascular: QT prolongation may occur. Avoid use in patients who are at significant risk of developing torsade de pointes, including those with congenital long QT syndrome, uncontrolled or significant cardiac disease, recent myocardial infarction, heart failure, unstable angina, bradyarrhythmias, AV block, aortic stenosis, or uncontrolled hypothyroidism. If use cannot be avoided, ECGs and monitoring required [1]
Concomitant use: Avoid use with products that increase the risk of QTc interval prolongation or concentrations of phenobarbital; monitoring required if use cannot be avoided [1].
Concomitant Use: Additive CNS depressant effects when used with alcohol or other CNS depressants [22].
Dermatologic: Necrosis may occur; avoid extravascular injection [23]. Interruption of therapy required [1]
Dermatologic: Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis and Stevens-Johnson syndrome, have been reported with phenobarbital; discontinuation and alternative therapy may be necessary [1].
Dermatologic: Transient pain to gangrene of the limb may occur; avoid intraarterial injection. Interruption of therapy required [1]
Endocrine and metabolic: Use caution in patients with hyperparathyroidism or diabetes mellitus [22]
Fever: Use caution in patients with fever [22]
Hematologic: Acute attacks of porphyria may occur and may be life-threatening when used in patients with acute porphyrias (unapproved used) [1]
Hematologic: Neonatal coagulation defects have been reported within the first 24 hours in neonates exposed during pregnancy (unapproved use) [1]
Hematologic: Use caution in patients with severe anemia [22]
Hepatic: Do not administer if hepatic coma is suspected [22].
Hepatic: Use with caution in patients with hepatic damage or severely impaired liver function; dosage adjustment may be necessary [22].
Immunologic: Drug reaction with eosinophilia and systemic symptoms (DRESS), also known as multiorgan hypersensitivity, including life-threatening and fatal cases, has been reported; evaluation and discontinuation may be necessary [1].
Immunologic: Hypersensitivity reactions may occur; evaluation and discontinuation may be necessary. Consider alternative therapies in patients with a personal or family history of hypersensitivity reactions to structurally similar drugs (eg, carboxamides [eg, carbamazepine] and hydantoins [eg, phenytoin]) [1]
Neurologic: Cognitive defects may occur in children for the treatment of complicated febrile seizures (unapproved use) [22].
Neurologic: Increased risk of marked excitement, depression, and confusion in debilitated patients [22]

Paradoxical reaction: Use in patients with acute or chronic pain may induce paradoxical excitement or mask symptoms [22].
Psychiatric: Use may increase the risk of suicidal thought or behaviors in adolescents and adults (unapproved populations) [1]
Renal: Use with extreme caution in patients with uremia [22].
Respiratory: Use with extreme caution in pulmonary disease or status asthmaticus [22].
Respiratory: Abnormal respiration has been reported; monitoring required [1]
Withdrawal: Abrupt cessation following prolonged use may result in withdrawal symptoms, including delirium, convulsions, and death [22]

Adverse Effects

Sedation at serum concentrations above 40 mcg/mL. Respiratory depression at concentrations above 60 mcg/mL. Irritating to veins - pH is approximately 10 and osmolality is approximately 15,000 mOsm/kg H_2O.

Common, younger than 14 days: Abnormal respiration (25%), sedation (16%), feeding disorder (16%), and hypotension (16%) [1]

Black Box Warning

IV Powder for Solution - Preservative-Free Formulation
Risks from Concomitant Use with Opioids[1]

- Concomitant use of phenobarbital products including phenobarbital sodium powder for solution, and opioids, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of these drugs for patients whom alternative treatment options are inadequate. If a decision is made for concomitant use of these drugs, limit dosages and durations to the minimum required, and follow patients for signs and symptoms of respiratory depression and sedation.

Dependence and Withdrawal Reactions After Use of Phenobarbital Sodium Powder for Solution for a Longer Duration than Recommended

- The continued use of phenobarbital may lead to clinically significant physical dependence. The risks of dependence and withdrawal increase with longer treatment duration and higher daily dose. Although phenobarbital sodium powder for solution is indicated only for short-term use, if used for a longer duration than recommended, abrupt discontinuation or rapid dosage reduction of phenobarbital sodium powder for solution may precipitate acute withdrawal reactions, which can be life-threatening. For patients receiving phenobarbital sodium powder for solution for longer duration than recommended, to reduce the risk of withdrawal reactions, use a gradual taper to discontinue phenobarbital sodium powder for solution.

Abuse, Misuse, and Addiction with Unapproved Use in Adolescents and Adults

- Phenobarbital sodium powder for solution is not approved for use in adolescent or adults. The unapproved use of phenobarbital sodium powder for solution, in adolescents and adults exposes them to risks of abuse, misuse, and addiction, which can lead to overdose or death. Abuse and misuse of phenobarbital commonly involve concomitant use of other drugs, alcohol, and/or illicit substances, which is associated with and

increased frequency of serious adverse outcomes.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Amikacin, aminophylline, caffeine citrate, calcium chloride, calcium gluconate, enalaprilat, fentanyl, fosphenytoin, heparin, ibuprofen lysine, linezolid, meropenem, methadone, morphine, propofol, and sodium bicarbonate.

Terminal Injection Site Incompatibility

Fat emulsion. Hydralazine, hydrocortisone succinate, insulin, methadone, pancuronium, ranitidine, and vancomycin. No data available on potassium chloride.

Monitoring

Therapeutic Laboratory Monitoring

• PHENobarbital monotherapy will control seizures in 43% to 85% of affected neonates - adding a second drug (phenytoin or lorazepam) is often needed. Therapeutic serum concentration is 15 to 40 mcg/mL. Drug accumulation may occur using recommended maintenance dose during the first two weeks of life. Altered (usually increased) serum concentrations may occur in patients also receiving phenytoin or valproate. In infants with neonatal abstinence syndrome, serum concentrations of 20 to 30 mcg/mL are associated with adequate symptom control.

Toxic Laboratory Monitoring

• Monitor serum electrolytes in patients at significant risk of developing torsade de pointes, including patients with congenital QT syndrome, uncontrolled or significant cardiac disease, recent myocardial infarction, heart failure, unstable angina, bradyarrhythmias, AV block, aortic stenosis, or uncontrolled hypothyroidism, if the use of phenobarbital cannot be avoided [1].

Toxic Physical Monitoring

• Observe IV site for signs of extravasation and phlebitis.
• Collect ECGs during treatment at specified intervals as clinically indicated in patients at significant risk of developing torsade de pointes, including patients with congenital QT

syndrome, uncontrolled or significant cardiac disease, recent myocardial infarction, heart failure, unstable angina, bradyarrhythmias, AV block, aortic stenosis, or uncontrolled hypothyroidism, if the use of phenobarbital cannot be avoided [1].
• Monitor for respiratory depression during and after the administration [1].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action: PHENobarbital exhibits gamma-aminobutyric acid (GABA)-like effects similar to benzodiazepines and reversibly depresses activity of all excitable tissue, however not all tissues are affected at equivalent doses of serum concentrations. PHENobarbital produces degrees of depression of the central nervous system from sedation to respiratory depression at different doses. The precise mechanism of action for PHENobarbital for the treatment of neonatal seizures is not fully understood, but it is thought to involve potentiation of synaptic inhibition through an action on the GABA A receptor [1]

Distribution
Vd: 0.64 to 1.17 L/kg in neonates [24].

Drug Concentrations
IV, multiple-dose, pre-term infants: A pilot study in 24 preterm infants (weight, less than 1500 g) administered a loading dose of PHENobarbital 15 mg/kg IV followed by 3 mg/kg/day 24 hours later, demonstrated that PHENobarbital concentrations were above 40 mcg/mL in 0%, 4.7%, 45.8%, 62.5%, and 70.8% of infants at 2-hours, 24-hours, 48-hours, 72-hours, and 96-hours after the administration of PHENobarbital [6].
IV, multiple dose (1 loading dose), term infants: 23 to 25 mcg/mL [1]
IV, multiple-dose (2 loading doses), term infants: 26 to 39 mcg/mL [1]

Metabolism
Substrate of: CYP2C9, CYP2C19, CYP2E1, and UGTs [1]
Inhibitor of: CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A4, UGT1A1, UGT2B7, BCRP, OAT1, OAT3, OCT2, OATP1B1, MATE1, and MATE2K [1]
Inducer of: CYP3A4, CYP2B6, CYP2Cs, and UGTs [1]

Excretion
Clearance: 0.0053 to 0.0141 L/hr/kg in neonates [24].

Elimination Half-Life
Half-life: 73.9 to 154.5 hours [24]; up to 1 week in neonates [1].

Extracorporeal Membrane Oxygenation (ECMO): Based on observed pharmacokinetic data in 7 neonates (median weight 3.5 kg) and 9 infants (median weight 8 kg) on ECMO, a simulation for PHENobarbital was suggested. For a loading dose of 15 mg/kg, 68.7% of neonates and infants were predicted to have PHENobarbital serum concentration between 10 to 40 mg/L and 31.2% would have concentrations above 40 mg/L. For a maintenance dose of 4 mg/kg/day, 87.5% of neonates and infants were predicted to have PHENobarbital serum

concentration between 10 to 40 mg/L and 12.5% would have concentrations above 40 mg/L. The following were the pharmacokinetic parameters for PHENobarbital in 7 neonates on ECMO [10]
Vd: mean, 0.46 L/kg (interquartile range 0.32 to 0.64 L/kg) [10]
CL: mean, 8 mL/kg/hr (interquartile range 5.2 to 9.3 L/kg/hr) [10]
Half-life: 46.1 hours (interquartile range 30.7 to 51.7 hours) [10]

ABOUT

Special Considerations/Preparation

Availability

Injection solution: Injectable solution available in concentrations of 60-, 65-, and 130-mg/mL, all containing 10% (100 mg/mL) alcohol and 67.8% propylene glycol [12].
Intravenous powder for Solution: Lyophilized powder in single-dose vials containing 100 mg of phenobarbital sodium. After reconstitution with 0.9% sodium chloride, the solution is preservative-free [1]
Oral: Oral solution is available in **20 mg/5 mL (4 mg/mL)** concentration; contains 13.5 % alcohol [4][25].

Storage/Stability

Injection solution: PHENobarbital sodium, diluted to 10 mg/mL in normal saline, was stable for 4 weeks under refrigeration [12].
Intravenous powder for solution: Store unopened vials in original carton at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F); excursions permitted between 15 and 30 degrees C (59 and 86 degrees F). Protect from light [1].
If not used immediately, the reconstituted solution may be stored in the original carton protected from light at a room temperature between 20 and 25 degrees C (68 and 77 degrees F) for a maximum of 8 hours or in the refrigerator between 2 and 8 degrees C (36 and 46 degrees F) for a maximum of 24 hours. Discard any unused portion after recommended storage duration [1].

Preparation

- Reconstitute lyophilized powder in vial using 10 mL of 0.9% sodium chloride [1]
- Swirl the vial gently until contents are completely dissolved [1]
- Withdraw the appropriate volume from the reconstituted vial for IV infusion and administer it immediately [1].

Standard Concentrations: The Institute for Safe Medication Practices (ISMP) and Vermont Oxford Network (VON) recommend a standard concentration of 10 mg/mL for neonatal patients weighing 500 g or more [26].

Extemporaneous Oral Suspension

10 mg/mL
To avoid alcohol content of the oral solution, an extemporaneous PHENobarbital suspension can be compounded by crushing ten (10) 60-mg tablets (600 mg total) into a fine powder. Mix 30 mL of Ora-Plus with 30 mL of either Ora-Sweet or Ora-Sweet SF. Add 15 mL to PHENobarbital powder and triturate. Transfer suspension to 2-ounce amber plastic bottle and

fill to final volume of 60 mL with Ora-Plus/Ora-Sweet mixture. Label "shake well before use," suspension stable for 115 days at room temperature [13].

Phentolamine

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Inject a 0.5-mg/mL solution of phentolamine subcutaneously into the affected area. Usual amount needed is 1 to 5 mL, depending on the size of the infiltrate. May be repeated if necessary.

Uses

Prevention of dermal necrosis and sloughing caused by extravasation of vasoconstrictive agents, eg, dopamine.

MEDICATION SAFETY

Contraindications/Precautions

Contraindications

• Myocardial infarction or history of myocardial infarction, coronary insufficiency, angina, or other evidence suggestive of coronary artery disease (IV, IM) [1]

Precautions

Administration: The parenteral blocking test is not the procedure of choice for screening tests in patients with hypertension and should be reserved for cases in which additional confirmatory evidence is necessary and the relative risks in conducting the test have been considered [1].

Cardiovascular: Myocardial infarction has been reported following parenteral administration, usually in association with marked hypotensive episodes [1][2].

Cardiovascular: Tachycardia and other cardiac arrhythmias may occur [1][2], Use caution in patients with a prior history of cardiovascular disease [2]. Administration of cardiac glycosides should be deferred until cardiac rhythm returns to normal [1].

Neurologic: Cerebrovascular spasm and occlusion have been reported following parenteral administration, usually in association with marked hypotensive episodes [1][2].

Adverse Effects

Hypotension could potentially occur if a very large dose is administered. Consider using topical 2% nitroglycerin ointment if affected extremity is significantly swollen.

Terminal Injection Site Compatibility

Amiodarone, dobutamine, and papaverine.

Monitoring

Assess affected area for reversal of ischemia. Monitor blood pressure.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Alpha-adrenergic blocking agent that produces peripheral vasodilation, thereby reversing ischemia produced by vasopressor infiltration. The effect should be seen almost immediately. Biological half-life when injected subcutaneously is less than 20 minutes.

ABOUT

Special Considerations/Preparation

Injection
Availability: 5 mg lyophilized powder for solution [1]
Storage
Store powder at a controlled room temperature between 20 and 25 degrees C (68 to 77 degrees F) with brief excursions permitted between 15 and 30 degrees C (59 to 86 degrees F). Use the reconstituted solution immediately; do not store [1].

Injection Preparation
1) Reconstitute one vial with 1 mL of normal saline [1].
2) Dilute to a concentration of 0.5 mg/mL with 9 mL normal saline. Use immediately [1].

Phenylephrine

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

IV
Hypercyanotic episodes associated with tetralogy of Fallot (tet spells):
IV bolus: 5 to 10 mcg/kg IV [1][2]
Continuous infusion: 2 to 5 mcg/kg/min [1]; titrate as needed to maintain adequate oxygenation and avoid hypotension [2]

Ophthalmic
1 drop instilled in the eye at least 10 minutes prior to funduscopic procedures.
Use **only** the 2.5% ophthalmic solution in neonates.
Apply pressure to the lacrimal sac during and for 2 minutes after instillation to minimize systemic absorption.

Uses

Ophthalmic
Induction of mydriasis for diagnostic and therapeutic ophthalmic procedures.

MEDICATION SAFETY

Adverse Effects

May cause decreased pulmonary compliance, tidal volume, and peak air flow in babies with BPD. Do not use in patients receiving beta-blocker medications (e.g. propranolol). The use of 10% solutions has caused systemic hypertension and tachycardia in infants.

Monitoring

Monitor heart rate and oxygen saturation in babies with BPD.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Alpha-adrenergic. Mydriasis begins within 5 minutes of instillation and lasts for 60 minutes. Without lacrimal sac occlusion, approximately 80% of each drop may pass through the nasolacrimal system and be available for rapid systemic absorption by the nasal mucosa.

ABOUT

Special Considerations/Preparation

Supplied as ophthalmic solution in 0.12%, 2.5%, and 10% concentrations in 2 to 15 mL quantities. Do not use solution that becomes discolored or contains precipitate. Refer to specific product or manufacturer's recommendation for storage.

A preparation containing cyclopentolate 0.2% and phenylephrine 1% (Cyclomydril®) is commercially available in 2- and 8-mL Drop-tainers.
A combination eye drop solution ("Caputo drops") may be prepared in a 15-mL bottle with 3.75 mL of cyclopentolate 2%, 7.5 mL of tropicamide 1%, and 3.75 mL of phenylephrine 10%. The final solution contains cyclopentolate 0.5%, tropicamide 0.5%, and phenylephrine 2.5%.
Use within 24 hours, as the solution contains no preservatives.

Phenytoin

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Loading dose: 15 to 20 mg/kg IV infusion.
Maintenance dose: 4 to 8 mg/kg every 24 hours IV slow push, or orally.
(Up to 8 mg/kg per dose every 8 to 12 hours after 1 week of age).

Dosage Adjustment
Pharmacogenomics
CYP2C9 intermediate or poor metabolizer: Reduce dose. No specific recommendations in pediatric patients; in adults the starting maintenance dose should be reduced by at least 25% in intermediate metabolizers and at least 50% in poor metabolizers. Dose adjustments are based on target phenytoin concentrations [1].
HLA-B*15:02 carrier: If phenytoin-naive, do not use [1].
HLA-B*15:02 noncarrier with normal CYP2C9 genotype: No dosage adjustment necessary [1].

Uses

Anticonvulsant often used to treat seizures refractory to phenobarbital.

Administration

Intravenous: Administer directly into a large peripheral or central vein through a large-gauge catheter. Administer 50 mg/mL (undiluted) at a rate of 1 to 3 mg/kg/minute (over approximately 15 to 20 minutes for loading dose and 10 minutes for maintenance dose); **maximum 50 mg/minute, which ever is slower**[2].
May dilute in normal saline at a concentration of no less than 5 mg/mL and infuse within 1 to 4 hours (60 to 240 minutes). If diluted in normal saline, then use an in-line filter (0.22 to 0.55 microns). Flush IV with saline before and after administration. Always inspect for particulate matter and discoloration before administration [2].
IM route not acceptable: poorly absorbed with drug crystallization in muscle; may cause necrosis of soft tissues at the injection site [3].

National Institute for Occupational Safety and Health (NIOSH) Recommendations
In the preparation and administration of injections, the National Institute for Occupational Safety and Health (NIOSH) recommends the use of double gloves and a protective gown. Prepare in a biological safety cabinet or a compounding aseptic containment isolator;

eye/face and respiratory protection may be needed. Prepare compounds in a closed system drug transfer device. During administration, if there is a potential that the substance could splash or if the patient may resist, use eye/face protection. Administer certain dosage forms via a closed system drug transfer device [4].
In the preparation of tablets or capsules, including cutting, crushing, or manipulating, or the handling of uncoated tablets, NIOSH recommends the use of double gloves and a protective gown. Prepare in a ventilated control device, if possible. Use respiratory protection if not prepared in a control device. During administration, wear single gloves, and wear eye/face protection if the formulation is hard to swallow or if the patient may resist, vomit, or spit up [4].
NIOSH recommends the use of double gloves and a protective gown by anyone handling a hazardous oral liquid or any hazardous drug via a feeding tube. Prepare in a control device, if possible. Use respiratory, eye, and face protection if not done in a control device. During administration, eye/face protection is needed if the patient may resist, or if there is potential to vomit or spit up [4].

Extravasation Management Neonatal data are limited to pooled data from 10 case reports/case series (n=237) and are not specific to phenytoin extravasation; subcutaneous saline irrigation with or without hyaluronidase infiltration was commonly used. No standardized management was established. An option for more severe injuries (stages 3 and 4) is subcutaneous irrigation with saline, but this is not advocated as standard treatment. Conservative management is appropriate for mild extravasation (stages 1 and 2) [5].
Although not neonatal-specific, the following are recommendations for extravasation of acidic or alkaline agents (phenytoin is alkaline with a pH of 10 to 12, greater than 700 mOsm/L) [6]

- **General:**
- Stop and disconnect infusion; do not remove the cannula or needle
- Attempt to gently aspirate as much extravasated agent as possible; avoid manual pressure
- Remove cannula or needle
- Dry heat and elevation
- Closely monitor for signs of coagulation and ischemia
- Avoid attempt at pH neutralization (phenytoin - pH 10 to 12)
- Alternate treatment, topical nitroglycerin 2% apply up to 1-inch strip to affected area every 8 hours as needed. Hypotension may occur as dosage may exceed those typically used for angina
- Monitor and consider the need for surgical management such as surgical flushing with normal saline or debridement and excision of necrotic tissue (especially if pain persists for 1 to 2 weeks). In cases of compartment syndrome, surgical decompression may be required
- **Refractory Events:**
- Hyaluronidase 15 units intradermally along injection site and edematous area. Give as five, 0.2-mL intradermal injections along extravasation site and edematous tissue.
- **Inadvertent Intraarterial Administration:**
- Leave inadvertent intraarterial line in place for diagnostics
- Systemic heparin titrated to therapeutic anticoagulant effect.

- Stellate ganglion block

MEDICATION SAFETY

Contraindications/Precautions

Contraindications
•Coadministration with delavirdine due to the potential for loss of virologic response and possible resistance to delavirdine or the class of NNRTI [10][11]
•History of prior acute hepatotoxicity attributable to phenytoin [10][11]
•History of hypersensitivity to phenytoin, its inactive ingredients, or other hydantoins [10][11].

Precautions
Cardiovascular: Bradycardia and cardiac arrest, including cases at recommended doses and phenytoin levels and those associated with toxicity, have been reported; cardiac arrest has occurred mostly in patients with underlying cardiac disease [12]
Concomitant use: Concomitant use of oral phenytoin with enteral feeding preparations not recommended [9][13][14].
Dermatologic: Soft tissue irritation and inflammation varying from slight injection site tenderness to extensive necrosis and sloughing, including "purple glove syndrome" with edema, discoloration, and pain distal to injection site, have been reported (even without extravasation); fasciotomies, skin grafting, or amputation may be necessary [9].
Dermatologic: Severe cutaneous adverse reactions (SCARs), including fatalities (eg, acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms [DRESS]) have been reported; discontinue use at the first sign of rash, unless clearly not drug-related, and evaluate patients for severe cutaneous reaction; do not reinitiate therapy if signs or symptoms suggest severe cutaneous reaction [12][11]
Dermatologic: Presence of HLA-B*1502 allele (more common in patients of Asian ancestry) or a decreased function CYP2C9*3 variant (more common in patients of southeast Asian ancestry) may increase risk of developing SCARs, including Stevens-Johnson syndrome or toxic epidermal necrolysis in patients taking antiepileptic drugs, including phenytoin; consider avoiding phenytoin as a carbamazepine alternative in patients positive for HLA-B*1502 [15][13]
Endocrine and metabolic: Hyperglycemia has been reported [9][16][13][14].
Endocrine and metabolic: Serum glucose levels may increase in patients with diabetes [9][16][13][14].
Hematologic: Thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, and pancytopenia with or without bone marrow suppression, including fatal cases, have been reported [9][16][13][14].
Hematologic: Use caution in patients with porphyria as exacerbation has been reported [9][16][13][14].
Hepatic: hyperbilirubinemia; bilirubin displaces phenytoin from protein-binding sites, resulting in increased serum free phenytoin concentration [17].
Hepatic: Patients with hepatic disease have an increased fraction of unbound phenytoin;

interpret total phenytoin plasma concentrations with caution [9].
Hepatic: Acute hepatotoxicity, including hepatic failure and fatalities, has been reported; discontinue and do not re-administer [9][16][13][14].
Hepatic: Phenytoin toxicity may occur in patients with impaired liver function or those who are gravely ill [9][16][13][14].
Immunologic: Drug reaction with eosinophilia and systemic symptoms (DRESS), also known as multiorgan hypersensitivity, including fatal cases, has been reported; evaluate patient if signs and symptoms are present and discontinue phenytoin if alternative etiology cannot be established [9][16][13][14].
Immunologic: Angioedema has been reported; discontinue immediately for presence of symptoms (facial, perioral, or upper airway swelling) [12][11]
Immunologic: Consider alternatives to structurally similar drugs such as carboxamides, barbiturates, succinimides, and oxazolidinediones in patients with a history of hypersensitivity to phenytoin [9][16][13][14].
Immunologic: Consider alternative to phenytoin in patients with personal or immediate family history of hypersensitivity to structurally similar drugs [9][16][13][14].
Immunologic: Local and generalized lymphadenopathy may occur; extended follow-up is recommended in all cases and alternative antiepileptic therapy should be utilized if possible [9][16][13][14].
Musculoskeletal: Decreased bone density and bone fractures have been reported, possibly due to increased metabolism of vitamin D and vitamin D deficiency; consider screening and initiating treatment if detected [16][13][14].
Neurologic: Delirium, psychosis, encephalopathy, or rarely irreversible cerebellar dysfunction may occur with concentrations above the therapeutic range; recommend plasma phenytoin levels at first sign of toxicity and dose reduction if excessive [9][16][13][14].
Pregnancy: A potentially life-threatening bleeding disorder may occur in neonates exposed to phenytoin in utero; administer vitamin K to mother prior to delivery and to neonate after birth [9][16].
Renal: Patients with renal disease have an increased fraction of unbound phenytoin; interpret total phenytoin plasma concentrations with caution [9].
Special populations: Avoid use in HLA-B*1502 carriers if patient is phenytoin/fosphenytoin-naive [1]. HLA-B*15:02-positive patients (most common in Asian patients) may have an increased risk of Stevens-Johnson syndrome and toxic epidermal necrolysis [18].
Special populations: Dose reduction and monitoring recommended in HLA-B*1502 non-carriers with intermediate or poor CYP2C9 metabolizer status [1].
Withdrawal: Abrupt withdrawal may precipitate increased seizure activity, status epilepticus. Dose reduction, discontinuation, or substitution of anticonvulsant therapy should be done gradually; if rapid withdrawal is necessary due to an allergic or hypersensitivity reaction, alternative therapy should not be in hydantoin class [9][16][13][14].

Adverse Effects

Extravasation causes tissue inflammation and necrosis due to high pH and osmolality. Propylene glycol content of the intravenous formulation has been associated with seizures and may potentiate the cardiovascular effects of phenytoin. Hypotension and cardiac arrhythmias have been reported. High serum concentrations are associated with seizures.

Dose related adverse events include nystagmus (total level 15 to 25 mg/L) and ataxia and mental status changes (total level greater than 30 mg/L). Movement disorders (bradykinesia and choreoathetosis) may also occur rarely. Hypersensitivity reactions have been reported in infants. Long-term effects of phenytoin include gingival hyperplasia, coarsening of the facies, hirsutism, hyperglycemia, and hypoinsulinemia. Cutaneous side effects include maculopapular exanthema, drug-induced lupus, and pigmentary alterations. Phenytoin interacts with carbamazepine, cimetidine, corticosteroids, digoxin, furosemide, phenobarbital, and valproate [7][19][3].

Supplementation with folic acid 0.5 mg/day orally was associated with a significantly lower rate of **gingival hyperplasia** (21% vs. 87.9% for placebo) in children 6 to 15 years of age taking phenytoin in a 6-month, randomized, double-blind, placebo controlled study (N=120) [20].

Black Box Warning

The rate of intravenous phenytoin administration should not exceed 1 to 3 mg/kg/min (or 50 mg per minute, whichever is slower) in pediatric patients because of the risk of severe hypotension and cardiac arrhythmias. Careful cardiac monitoring is needed during and after administering intravenous phenytoin. Although the risk of cardiovascular toxicity increases with infusion rates above the recommended infusion rate, these events have also been reported at or below the recommended infusion rate. Reduction in rate of administration or discontinuation of dosing may be needed [9].

Solution Compatibility

NS only.

Solution Incompatibility

D_5W and $D_{10}W$.

Terminal Injection Site Compatibility

Esmolol, famotidine, and fluconazole.

Terminal Injection Site Incompatibility

Amikacin, cefepime, ceftazidime, chloramphenicol, clindamycin, dobutamine, enalaprilat, fentanyl, heparin, hyaluronidase, hydrocortisone succinate, insulin, lidocaine, linezolid, methadone, micafungin, morphine, nitroglycerin, pentobarbital, potassium chloride, procainamide, propofol, sodium bicarbonate, and vitamin K_1.

Monitoring

Monitor electrocardiogram, blood pressure, and respiratory function continuously during infusion, and for 15 minutes to 1 hour after infusion [7][8]. Observe IV site for extravasation. Follow serum concentration closely: therapeutic range is 6 to 15 mcg/mL in the first weeks, then 10 to 20 mcg/mL due to changes in protein binding. Obtain initial trough level 48 hours after IV loading dose.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Hepatic metabolism capacity is limited; saturation may occur within therapeutic range. Pharmacokinetics are dose-dependent. Elimination rate is increased during first few weeks of life. Serum half-life is 18 to 60 hours. 85% to 90% protein bound. Bilirubin displaces phenytoin from protein-binding sites, resulting in increased serum free phenytoin concentration [21][22][23][17][24].
In neonates, oral and IV phenytoin doses resulted in similar serum concentrations [25].

ABOUT

Special Considerations/Preparation

Injectable solution: 50 mg/mL. Contains 0.4 mL/mL of propylene glycol and 0.1 mL/mL of alcohol. For IV infusion, dilute in NS to a final concentration of no less than 5 mg/mL. Do not refrigerate diluted solution [7].
Oral suspension: 25 mg/mL [26].

Extemporaneous Compound
15 mg/mL Oral Suspension [27]

- Phenytoin, as an active pharmaceutical ingredient, was compounded with SyrSpend® SF PH4 to make a 15 mg/mL suspension
- Stable for 90 days at refrigeration (2 to 8 degrees C) and room temperature (20 to 25

degrees C)

- Shake suspension for 1 minute before measuring dose

Piperacillin

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

50 to 100 mg/kg/dose IV infusion or IM.

Antibiotic Dosing Chart:
Renal function and drug elimination are most strongly correlated with Postmenstrual Age (PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.

Dosing Interval Chart		
PMA (weeks)	**PostNatal (days)**	**Interval (hours)**
≤29	0 to 28 >28	12 8
30 to 36	0 to 14 >14	12 8
37 to 44	0 to 7 >7	12 8
≥45	ALL	6

Uses

Semisynthetic penicillin with increased activity against *Pseudomonas aeruginosa* and many strains of *Klebsiella, Serratia, E coli, Enterobacter, Citrobacter,* and *Proteus.* Also effective against group B *Streptococcus*.

Administration

Intravenous: For IV infusion, dilute reconstituted solution to a concentration of less than or equal to 40 mg/mL and infuse over 30 minutes [1].

MEDICATION SAFETY

Adverse Effects

Eosinophilia. Hyperbilirubinemia. Elevations in ALT, AST, BUN, and serum creatinine.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Acyclovir, aminophylline, aztreonam, clindamycin, enalaprilat, esmolol, famotidine, heparin, hydrocortisone succinate, linezolid, lorazepam, magnesium sulfate, midazolam, milrinone, morphine, nicardipine, potassium chloride, propofol, ranitidine, remifentanil, and zidovudine.

Terminal Injection Site Incompatibility

Amikacin, amiodarone, gentamicin, netilmicin, fluconazole, tobramycin, and vancomycin.

Monitoring

Desired peak serum concentration is approximately 150 mcg/mL.
Desired trough concentration ranges from 15 to 50 mcg/mL (available as bioassay). Peak serum concentration is lower with IM administration. Observe IV site for signs of extravasation.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Piperacillin is a potent, broad-spectrum, semi-synthetic, ureidopenicillin possessing high activity against gram-negative bacteria. Inactivation by beta-lactamase-producing bacteria. Synergistic with aminoglycosides. Good penetration into bone; CSF penetration similar to that of other penicillins. Serum half-life depends on gestational age and postnatal age. Primarily excreted renally unchanged.

ABOUT

Special Considerations/Preparation

Available as powder for injection in 2-g, 3-g, 4-g, and 40-g vials. Reconstitute 2-g vial with 10 mL of sterile water for injection to make a final concentration of 200 mg/mL. Reconstituted solution stable for 24 hours at room temperature, 2 days refrigerated. A 50 mg/mL dilution may be made by adding 2.5 mL of reconstituted solution to 7.5 mL sterile water for injection. Dilution stable for 2 days refrigerated.

IM Administration : Use 400 mg/mL concentration.

Piperacillin/Tazobactam

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Dosing in neonates is based on limited pharmacokinetic studies [1][2][3].

PMA (weeks)	Postnatal	Dose IV * †	Interval
29 weeks or less	0 to 28 days	100 mg/kg/dose	12 hours
	greater than 28 days		8 hours
30 to 36 weeks	0 to 14 days	100 mg/kg/dose	12 hours
	greater than 14 days		8 hours
37 to 44 weeks	0 to 7 days	100 mg/kg/dose	12 hours
	greater than 7 days		8 hours
45 weeks or more	ALL	100 mg/kg/dose	8 hours
PMA = Postmenstrual age (PMA equivalent to gestational age plus postnatal age). PMA is the primary determinant of dosing interval, with postnatal age as the secondary qualifier.			
*Dose for piperacillin component			
Cohen-Wolkowiez, 2014			

† Target concentrations were achieved (unbound piperacillin concentrations for 75% of the dosing interval) in 78%, 75%, and 90% of dose simulations at MICs of 32 mg/L, 16 mg/L, and 8 mg/L or less, respectively [2].

Dose Adjustments
Renal impairment
Dosage adjustment is recommended; there are no data available to provide dose recommendations for neonate patients with renal impairment[4].

Uses

Infective endocarditis: The following recommendations are based on a consensus of experts [6]. The full pediatric guidelines can be found here: https://doi.org/10.1161/CIR.0000000000000298

Organism Directed Therapy		
Organism	First-Choice	Alternative Choice
Streptococci		
Highly susceptible to penicillin G (MBC 0.1 mcg/mL or less); includes most viridans streptococci, groups A, B, C, G nonenterococcal, group D streptococci (S bovis, S equinus)	Penicillin G or CefTRIAXone	Vancomycin or First-generation cephalosporin or CefTRIAXone
Relatively resistant to penicillin (MBC 0.2 mcg/mL or more); less-susceptible viridans streptococci or enterococci	Penicillin G or Ampicillin + Gentamicin (for first 2 weeks, or entire course for enterococci)	Vancomycin + Gentamicin for enterococci Ampicillin + CefTRIAXone (for aminoglycoside (AMG)-resistant enterococci or AMG-intolerant patient) CefTRIAXone + gentamicin (not for enterococcal endocarditis)
Resistant to penicillin	Consult an infectious disease specialist.	---
Staphylococci (S aureus or coagulase-negative staphylococci) †		
Penicillin G susceptible (1 mcg/mL or less) (rare)	Penicillin G	Oxacillin or Nafcillin or First-generation cephalosporin or Vancomycin
Penicillin G resistant (0.1 mcg/mL)	Oxacillin or Nafcillin with or without Gentamicin	Vancomycin (for those highly allergic to beta-lactam antibiotics) or First-generation

		cephalosporin
Oxacillin (MRSA) resistant (4 mcg/mL)	Vancomycin	Daptomycin for right-sided endocarditis, maybe for left-sided
Vancomycin resistant or intolerant	Daptomycin	Unknown
	†When prosthetic material present add riFAMpin + gentamicin (for first 2 weeks) for all staphylococci	
Gram-negative enteric bacilli	CefTAZidime or Cefepime or Cefotaxime or CefTRIAXone Plus gentamicin (or tobramycin or amikacin, depending on susceptibility)	Broad-spectrum penicillin Plus gentamicin (or tobramycin or amikacin)
HACEK group	CefTRIAXone or Cefotaxime or Ampicillin-sulbactam	Ampicillin (when susceptible) Plus aminoglycoside
KEY: AMG = aminoglycosides; HACEK = Haemophilus species, Aggregatibacter species, Cardiobacterium hominis, Eikenella corrodens, and Kingella species; MBC = minimum bactericidal concentration, MRSA = methicillin-resistant Staphylococcus aureus (includes resistance to oxacillin, nafcillin, and cephalosporins)		
Baltimore, 2015		

Pediatric FDA Approved Indications

Piperacillin/tazobactam is not approved for newborn infants.

In children 2 months or older, piperacillin/tazobactam is approved for appendicitis (complicated by rupture or abscess) and peritonitis caused by β-lactamase producing isolates of *Escherichia coli* or the following members of the *Bacteroides fragilis* group: *B fragilis*, *B ovatus*, *B thetaiotaomicron*, or *B vulgatus*[7].

In children 2 months or older, piperacillin/tazobactam is approved for nosocomial pneumonia (moderate to severe) caused by β-lactamase producing isolates of *Staphylococcus aureus*, piperacillin/tazobactam-susceptible *Acinetobacter baumannii* , *Haemophilus influenzae*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* (in combination with an

aminoglycoside for nosocomial pneumonia caused by *P aeruginosa*) [7]
Additional approved indications in adults: uncomplicated and complicated skin and skin structure infections, including cellulitis, cutaneous abscesses and ischemic/diabetic food infections caused by β-lactamase producing isolates of *Staphylococcus aureus*; postpartum endometritis or pelvic inflammatory disease caused by β-lactamase producing isolates of *E coli*; community-acquired pneumonia (moderate severity only) caused by β-lactamase producing isolates of *Haemophilus influenzae*[7].

Administration

Infuse IV over at least 30 minutes [5].
Discontinue primary infusion solution during piperacillin/tazobactam infusion. [5]

MEDICATION SAFETY

Contraindications/Precautions

CONTRAINDICATIONS
Contraindicated in patients with a history of hypersensitivity reactions to any of the penicillins, cephalosporins, or beta-lactamase inhibitors [4].

PRECAUTIONS
Concomitant Use: Probenecid not recommended unless benefit outweighs risk [4]
Dermatologic: Serious cutaneous reactions (eg, Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis) have been reported; close monitoring recommended and discontinue if lesions progress [4]
Endocrine and metabolic: Hypokalemia may occur especially in patients with low potassium reserves and concomitant diuretic or cytotoxic therapy; monitoring recommended in patients with low potassium reserves [4]
Endocrine and metabolic: Use caution in patients requiring sodium restriction as product contains 2.84 mEq (65 mg) of sodium per g of piperacillin [4].
Gastrointestinal: Clostridium difficile-associated diarrhea, including mild diarrhea to fatal colitis, has been reported and may occur more than 2 months after use; discontinuation of antibacterial use not directed against C. difficile may be required [4]
Hematologic: Bleeding manifestations have been reported with piperacillin use, especially in patients with renal failure; monitoring recommended particularly with prolonged use (ie, 21 days or greater); discontinue use if occurs [4]
Hematologic: Leukopenia and neutropenia have been reported, especially with prolonged use; usually reversible upon discontinuation; however, monitoring recommended [4]
Immunologic: Serious anaphylactic reactions, with some fatal cases, have been reported, especially in patients with history of penicillin, cephalosporin, or carbapenem hypersensitivity or history of sensitivity to multiple allergens [4]
Immunologic: Hemophagocytic lymphohistiocytosis has been reported in adult and

pediatric patients; if suspected, discontinuation required and institute appropriate management [8].
Neurologic: Neuromuscular excitability or convulsions may occur at higher than recommended doses, particularly in the presence of renal failure [9].
Renal: Increased risk of nephrotoxicity in critically ill patients, including renal failure and delayed recovery of renal function; consider alternative therapy, otherwise monitoring required during treatment [10].
Renal: Use caution in patients with renal failure; increased risk of neuromuscular excitability or convulsions with higher than recommended IV doses [4]
Renal: Renal insufficiency (ie, CrCl less than or equal to 40 mL/min) and hemodialysis or continuous ambulatory peritoneal dialysis patients; dosage adjustments required [4]
Respiratory: Use caution in patients with cystic fibrosis due to increased risk for fever and rash [4]

Adverse Effects

Common adverse events (greater than 5%) in adults were diarrhea, constipation, nausea, headache, and insomnia [4].

Monitoring

Monitor electrolytes periodically in patients with low potassium reserves. Consider monitoring electrolytes periodically in patients with potentially low potassium reserves or those receiving cytotoxic therapy or diuretics. Periodic assessment of hematopoietic function, especially with prolonged therapy of 21 days or greater [4].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Piperacillin/tazobactam combines the extended-spectrum antibiotic piperacillin with the beta-lactamase inhibitor tazobactam.

Distribution: Both piperacillin and tazobactam were 30% bound to plasma proteins. Mean tissue concentrations were typically 50% to 100% of plasma concentrations. In non-inflamed meninges, distribution of piperacillin and tazobactam into CSF was low [4].
Excretion: Both piperacillin and tazobactam were eliminated by glomerular filtration and tubular secretion. Piperacillin was excreted rapidly as unchanged drug (68% excreted unchanged). Tazobactam and its metabolite was eliminated primarily by renal excretion (80% excreted unchanged) [4].

Neonatal Pharmacokinetics

Gestational Age	Postnatal Age	CL (L/hr/kg)	V (L/kg)	Half-life (hours)
less than 32 weeks	younger than 14 days (n=12)	0.055 (0.034 to 0.137)	0.42	5.3 (2.1 to 8.6)
	14 days or older (n=9)	0.116 (0.033 to 0.142)	0.42	2.5 (2.1 to 8.9)
32 weeks or more	younger than 14 days (n=8)	0.104 (0.063 to 0.142)	0.42	2.8 (2.1 to 4.6)
	14 days or older (n=3)	0.065 (0.062 to 0.177)	0.42	4.5 (1.7 to 4.7)
Overall (n=32)		0.085 (0.033 to 0.177)	0.42	3.5 (1.7 to 8.9)
Data are median (range) population parameter estimate				
Cohen-Wolkowiez, 2014				

Clearance of piperacillin/tazobactam is significantly associated with body weight, postmenstrual age, postnatal age, and serum creatinine [2].
The population parameter estimates for piperacillin in 32 neonates administered piperacillin/tazobactam 240 mg/kg/day (piperacillin component) IV divided every 8 hours (3 of the oldest infants (14 days or older and 32 weeks or more gestational age) received 300 mg/kg/day) administered over 30 minutes is in the tables below [2]:

Cohort		Predicted Piperacillin Concentrations at Steady State		
Gestational Age	Postnatal Age	Cmin (mg/L)	Concentration for 75% of the dosing interval (mg/L)	Concentration for 50% of the dosing interval (mg/L)
less than 32 weeks	younger than 14 days (n=12)	38.3 (7.4 to 48.4)	51.9 (16.9 to 58.9)	71.1 (38.6 to 75.6)
	14 days or older (n=9)	34.6 (5.5 to 48.4)	48.5 (13.5 to 58.9)	69.1 (33.6 to 75.6)
32 weeks or more	younger than 14 days	28 (1.3 to 48.4)	41.9 (4.7 to 58.9)	64.3 (17 to 75.6)

	(n=8)			
	14 days or older (n=3)	31.1 (1.5 to 60.2)	48.2 (5.7 to 73.4)	76.6 (20.7 to 94.5)
Overall (n=32)		30.1 (1.3 to 60.2)	44.1 (4.7 to 73.4)	66.2 (17 to 94.5)
Data are median (range)				
Cohen-Wolkowiez, 2014				

Target concentrations were achieved (unbound piperacillin concentrations for 75% of the dosing interval) in greater than 90% of dose simulations at MICs of less than 8 mg/L up to 32 mg/L with the following dosages 100 mg/kg/dose IV every 8 hours for PMA of 30 weeks or less, 80 mg/kg/dose IV every 6 hours for PMA of 31 to 35 weeks, and 80 mg/kg/dose IV every 4 hours for PMA 36 to 49 weeks [2].

Extended-infusion (over 2 to 4 hours) did not improve target concentrations compared with standard infusion (30 minutes) in a model-based simulation in neonates [2].

ABOUT

Special Considerations/Preparation

Availability

• Available as powder for injection (containing EDTA and sodium citrate) in 2.25-g, 3.375-g, and 4.5-g single-dose vials and 40.5-g pharmacy bulk vials. Each vial provides 2 g, 3 g, 4 g, and 36 g of piperacillin for the 2.25-g, 3.375-g, and 4.5-g single-dose vials and 40.5-g pharmacy bulk vials, respectively [5].
• Each 2.25-g, 3.375-g, 4.5-g vial, and 40.5-g bulk vial contains 5.68, 8.52, 11.36 mEq, and 100.4 mEq (130, 195, 260, 2304 mg) of sodium, respectively [5].
• Available in Galaxy® containers (containing EDTA and sodium citrate) as 2.25 g/50 mL, 3.375 g/50 mL, and 4.5 g/100 mL [5].
• Available as powder for injection in 2.25-g, 3.375-g, and 4.5-g ADD-Vantage® vials [11].

Preparation

Single- and multiple-use vials

• Reconstitute initially with NS, D5W, sterile water for injection, bacteriostatic saline or water with parabens, or bacteriostatic saline or water with benzyl alcohol. Use 10 mL, 15 mL, 20 mL, and 152 mL of diluent with 2.25 g, 3.75 g, 4.5 g, and 40.5 g piperacillin/tazobactam, respectively. After reconstitution, the concentrations will be 202.5 mg/mL (180 mg/mL piperacillin and 22.5 mg/mL tazobactam) for the single-dose vials and 225 mg/mL (200 mg/mL piperacillin and 25 mg/mL tazobactam) for the multiple-dose vials [5].
• For patients weighing **more than 40 kg**, dilute further to 50 to 150 mL with NS, D5W, sterile water for injection (maximum volume 50 mL), dextran 6% in saline, or LR (only for use with piperacillin/tazobactam containing EDTA and is compatible for coadministration via a Y-site) [5].

• For patients weighing **40 kg or less**, dilute further to final concentration of 22.5 mg/mL (piperacillin 20 mg/mL and tazobactam 2.5 mg/mL) to 90 mg/mL (piperacillin 80 mg/mL and tazobactam 10 mg/mL) with NS, D5W, sterile water for injection (maximum volume 50 mL), dextran 6% in saline, or LR (only for use with piperacillin/tazobactam containing EDTA and is compatible for coadministration via a Y-site) in an appropriately sized syringe or IV bag [5].
• Following reconstitution, discard any unused portion after 24 hours if stored at room temperature (20 to 25 degrees C [68 to 77 degrees F]) or after 48 hours if refrigerated (2 to 8 degrees C [36 to 46 degrees F]) [5].
• Chemical stability in IV bags has been demonstrated for up to 24 hours at room temperature and for up to 1 week under refrigeration [5].
• Do not add to blood products [5].
•**Ambulatory IV infusion pumps**. Reconstitute and dilute each dose to a volume of **25 or 37.5 mL** with a compatible solution. Stable for 12 hours at room temperature [5].

Preparation
Galaxy® Containers
• If the dose required does not equal 2.25 g, 3.375 g, or 4.5 g, piperacillin/tazobactam injection in Galaxy containers is not recommended for use; consider an alternative formulation [5].
• Frozen product containers may be fragile in frozen state, handle frozen product containers with care [5].
• Thaw container at room temperature (20 to 25 degrees C [68 to 77 degrees F]) or under refrigeration (2 to 8 degrees C [36 to 46 degrees F]); do not use water baths or microwave to thaw [5].
• Thawed solution is stable for up to 14 days when refrigerated (2 to 8 degrees C [36 to 46 degrees F]), or for 24 hours at room temperature (20 to 25 degrees C [68 to 77 degrees F]); do not refreeze after thawing [5].
• Do not use plastic container in series connections due to risk of air embolism [5].

Preparation
Hospira, Inc ADD-Vantage® system
• Do not refrigerate or freeze after reconstitution; solution is stable at room temperature for up to 24 hours [11].
• Do not use the flexible container in series connections [11].

Poractant alfa

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Respiratory Distress Syndrome
Initial dose: 2.5 mL/kg/dose (200 mg/kg/dose) intratracheally, administered as 1 or 2 aliquots depending upon the instillation procedure [1]
May be followed by up to 2 subsequent doses of 1.25 mL/kg/dose (100 mg/kg/dose) administered approximately every 12 hours if needed [1]; typically administer no more frequently than every 12 hours, unless surfactant is being inactivated by an infectious process, meconium, or blood [2]. For rescue therapy, administer as soon as possible, preferably within 2 hours after birth. For prophylactic therapy, administer after initial resuscitation but within 10 to 30 minutes after birth [2].
Maximum dosage: Sum of initial and up to 2 repeat doses, 5 mL/kg (400 mg/kg) [1]

Uses

Respiratory distress syndrome (RDS) in premature infants: It is strongly recommended that CPAP immediately after birth with subsequent selective surfactant administration be considered as an alternative to routine intubation with prophylactic or early surfactant administration in preterm infants. Severe RDS in preterm infants born younger than 30 weeks gestation who need mechanical ventilation should be administered surfactant after initial stabilization. Consider the use of rescue surfactant for infants with hypoxic respiratory failure attributable to secondary surfactant deficiency, such as meconium aspiration syndrome or sepsis/pneumonia[2].
Comparative Trials: Animal-derived surfactants (beractant, calfactant, and poractant alfa) had comparable outcomes for air leak syndromes, death, and bronchopulmonary dysplasia in a retrospective study (n=51,282; median birth weight of 1435 g; median gestation age of 30 weeks (27 to 33 weeks)) [3]. In a prospective randomized trial, the animal-derived surfactants all improved FiO2 need, PaO2 values, chest x-ray findings, and lung ultrasonography (LUS) scores (N=62, gestational age range 24 to 34 weeks, birthweight range 560 to 2500 g). However, the results were significantly better with poractant alfa and beractant compared with calfactant. The FiO2 values at 24 hours post-surfactant for poractant alfa, beractant, and calfactant were 36.8%, 33.6%, and 53.1%, respectively. The PaO2 values at 24 hours post-surfactant for poractant alfa, beractant, and calfactant were 64.7, 66.3, and 61.3 mmHg, respectively. The LUS scores at 24 hours post-surfactant for poractant alfa, beractant, and calfactant were 3.8, 4.3, and 6.9, respectively. Significantly more calfactant-treated patients required repeat dosing. Mechanical ventilation duration and hospital length of stay were similar between all 3 groups [4].

Late Administration: Poractant administered at 2 weeks of age in very preterm infants (less than 33 weeks' gestation) on ventilation did not reduce the duration of ventilation;

however, the rehospitalization rate for respiratory problems after discharge at 1 year of age was reduced (28.3% vs 51.1%; p=0.03) in a randomized, double-blinded, controlled, multicenter trial (n=118). The dosage of poractant was 2.5 mL/kg (200 mg/kg) [5].

Neonatal FDA-Approved Indications
Indicated for the treatment (rescue) of respiratory distress syndrome in premature infants. Poractant alfa reduced mortality and pneumothoraces associated with RDS [1].

Administration

For Endotracheal Tube Instillation Using a 5-French end-hole Catheter
•May suction the endotracheal tube before administration of surfactant [1]
•Slowly withdraw the entire contents of the vial into a 3 or 5 mL plastic syringe through a large-gauge needle (e.g., at least 20 gauge); enter each single-use vial only once [1]
•Attach the 5 French end-hole catheter of appropriate length to position the catheter tip proximal to the distal portion of the endotracheal tube, to the syringe. Fill the catheter with poractant alfa suspension. Discard excess poractant alfa through the catheter so that only the dose to be given remains in the syringe [1]
•First aliquot: Keep infant in neutral position, right or left side dependent. Immediately before administration, ventilate the infant with supplemental oxygen to maintain SaO(2) greater than 92%. Insert catheter into the endotracheal tube and instill the first aliquot, then remove catheter and manually ventilate with supplemental oxygen until stable [1]
•Second aliquot: When the infant is stable, reposition the infant such that the other side is dependent. Administer the remaining aliquot using the same procedure as the first aliquot. After completion of the dosing procedure, do not suction airways for 1 hour after surfactant instillation unless signs of significant airway obstruction occur [1]

For Endotracheal Tube Instillation Using the Second Lumen of a Dual Lumen Endotracheal Tube without Interrupting Ventilation
•May suction the endotracheal tube before administration of surfactant [1]
•Slowly withdraw the entire contents of the poractant alfa suspension vial into a 3 or 5 mL plastic syringe through a large-gauge needle (e.g., at least 20 gauge). Do not attach 5 French end-hole catheter. Remove the needle and discard excess poractant alfa suspension so that only the dose to be given remains in the syringe [1].
•Keep the infant in a neutral position (head and body in alignment without inclination). Administer poractant alfa suspension through the proximal end of the secondary lumen of the endotracheal tube as a single dose, given over 1 minute, and without interrupting mechanical ventilation [1].
•After completion of this dosing procedure, ventilator management may require transient increases in FiO2 , ventilator rate, or PIP. Do not suction airways for 1 hour after surfactant instillation unless signs of significant airway obstruction occur [1].

MEDICATION SAFETY

Contraindications/Precautions

Contraindications

Specific contraindications have not been determined[1]

Precautions

Administration: Transient events (including bradycardia, hypotension, endotracheal tube blockage, and oxygen desaturation) may occur; stop administration and treat as needed, when patient is stable may continue dosing with appropriate monitoring [1]
Respiratory: Exogenous surfactants can rapidly affect oxygenation and lung compliance; monitoring required [1]

Adverse Effects

Transient episodes of reflux of bradycardia, hypotension, endotracheal tube blockage, and oxygen desaturation have been reported during administration [6].

Monitoring

Monitor clinical and laboratory tests frequently for appropriate oxygen therapy and ventilatory support [6].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Pulmonary lung surfactants are essential for effective ventilation by modifying alveolar surface tension thereby stabilizing the alveoli. Curosurf® is an extract of natural porcine lung surfactant consisting of 99% polar lipids (mainly phospholipids) and 1% hydrophobic low molecular weight proteins (surfactant associated proteins SP-B and SP-C). Each mL of surfactant contains 76 mg of phospholipids calculated from the content of phosphorus (55 mg of phosphatidylcholine of which 30 mg is dipalmitoyl phosphatidylcholine) and 1 mg of protein including 0.45 mg of SP-B and 0.59 mg of SP-C [1].

ABOUT

Special Considerations/Preparation

Availability: 1.5 mL (120 mg poractant alfa) and 3 mL (240 mg poractant alfa) vials [1]
Storage: Refrigerate at 2 to 8 degrees C (36 to 46 degrees F) and protect from light. Inspect Curosurf® for discoloration; normal color is creamy white. If settling occurs during storage, gently turn vial upside-down in order to uniformly suspend. **Do not shake.** Used vials with residual drug should be discarded. Unopened vials that have been warmed to room temperature one time may be refrigerated within 24 hours and stored for future use. Should not be warmed and returned to the refrigerator more than once [1].

Preparation
•Slowly warm vial to room temperature before administration [1]
•Discard if suspension discolored (other than white to creamy white) [1]
•Gently turn vial upside down to obtain a uniform suspension; do not shake [1]

Potassium chloride

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Initial oral replacement therapy: 0.5 to 1 mEq/kg/day orally divided and administered with feedings (small, more frequent aliquots preferred). Adjust dosage based on monitoring of serum potassium concentrations.

1 g KCl = 13.4 mEq K^+1 mEq K^+ = 74.6 mg KCl

Acute treatment of symptomatic hypokalemia: Begin with 0.5 to 1 mEq/kg IV over 1 hour, then reassess.

Daily Requirement: 2 to 4 mEq/kg/day IV of potassium [1],

Uses

Treatment of hypokalemia.

Administration

Maximum infusion rate 1 mEq/kg/hour [2][3]. Preferred concentration for peripheral infusion is 40 mEq/L; **maximum concentration for peripheral infusion 60 to 80 mEq/L**[2][4][5][6][7]. A **maximum concentration of 200 mEq/L for central line** infusion has been suggested [8]

MEDICATION SAFETY

Contraindications/Precautions

Contraindicated in patients with renal failure. Rapid IV infusions, especially concentrated solutions through central lines, may cause arrhythmias including heart block and cardiac arrest. Peripheral IV administration of concentrated potassium solutions is associated with thrombophlebitis and pain at the injection site; central line should be used for concentrated solutions. Other signs of potassium toxicity include paresthesia of the extremities, weakness, and mental confusion [9][7].

Adverse Effects

GI irritation is common--most commonly diarrhea, vomiting, and bleeding-- minimized by dividing oral doses and administering with feedings. Use with caution (if at all) in patients receiving potassium-sparing diuretics, e.g. spironolactone [9][7].

Solution Compatibility

Most standard IV solutions.

Terminal Injection Site Compatibility

Most drugs.

Terminal Injection Site Incompatibility

Amphotericin B, diazepam, and phenytoin.

Monitoring

Continuous EKG monitoring is mandatory if administering by the IV route, especially for central infusions. Observe IV site closely for signs of extravasation when using concentrated solutions. Monitor serum potassium concentration. Assess for GI intolerance.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Potassium is the major intracellular cation. Hypokalemia in critically ill neonates is usually the result of diuretic (furosemide, thiazides) therapy or diarrhea. Other causes include congenital adrenal hyperplasia and renal disorders. Alkalosis, as well as insulin infusions, will lower

serum potassium concentrations by driving the ion intracellularly. Symptoms of hypokalemia include neuromuscular weakness and paralysis, ileus, urine retention, and EKG changes (ST segment depression, low-voltage T wave, and appearance of U wave). Hypokalemia increases digitalis toxicity. Oral potassium preparations are completely absorbed.

ABOUT

Special Considerations/Preparation

Potassium chloride for injection is supplied as 2-mEq/mL solution. **Always dilute before administration.** Hyperosmolar - 4355 mOsm/kg determined by freezing-point depression. pH ranges from 4 to 8 depending on buffering. Various oral solutions are available, with concentrations ranging from 10 to 40 mEq per 15 mL. Other oral forms available include powder packets, tablets, and sustained-release capsules.

Potassium Iodide

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Prevent Injury to Thyroid Gland Due to Radiation Emergency
Use under the direction of public officials [1]
16.25 mg orally every day [1]

Uses

Nuclear Radiation Emergency: Helps prevent radioactive iodine from getting into the thyroid gland during a nuclear radiation emergency (Thyroshield®)[1].

Pediatric FDA Approved Indications
Safety and effectiveness in children have not been established for saturated solution of potassium iodide (SSKI®) [2]

MEDICATION SAFETY

Contraindications/Precautions

Precautions
Cardiac: Use with caution in patients with cardiac disease [2].
Endocrine and Metabolic: May cause overactive thyroid gland, underactive thyroid gland, or enlargement of thyroid gland (goiter). Newborns are more like to experience an underactive thyroid gland [1].
Endocrine and Metabolic: Prolonged use can lead to hypothyroidism [2].
Endocrine and Metabolic: Use with caution in patients with Addison's disease or hyperthyroidism [2].
Musculoskeletal: Use with caution in patients with myotonia congenita [2].
Renal: Use with caution in patients with renal function impairment [2].
Respiratory: Use with caution in patients with tuberculosis or acute bronchitis [2].
Endocrine and Metabolic: Newborns are more like to experience an underactive thyroid gland [1].
Immunologic: Allergic reactions may occur [1].

Adverse Effects

Swelling or tenderness of salivary glands, nausea, vomiting, diarrhea, stomach ache, fever, headache, metallic taste, and allergic reactions [1].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Thyroid blocking [1].

ABOUT

Special Considerations/Preparation

Availability: 65 mg/mL potassium iodide oral solution over-the-counter product (used in the prevention of injury to the tyroid gland due to a radiation emergency) [1]; 1 g/mL of saturated solution of potassium iodide (SSKI) [2]

Storage: Protect from light [1][2].

Procainamide

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Initial bolus dose: 7 to 10 mg/kg IV.

Maintenance IV infusion: 20 to 80 mcg/kg per minute. Premature neonates should receive the lowest dose.

Uses

Acute treatment of supraventricular tachycardia (SVT) refractory to vagal maneuvers and adenosine. Acute treatment of ventricular tachycardia unresponsive to cardioversion and adenosine. Ectopic tachycardia, junctional ectopic tachycardia, and atrial flutter. Consider obtaining expert consultation before use.

Administration

Intravenous/Intraosseous: Administer loading dose over 30 to 60 minutes at a concentration of 20 mg/mL. For continuous infusion, administer at a concentration of 2 to 4 mg/mL [1][2][3].

MEDICATION SAFETY

Contraindications/Precautions

Contraindicated in patients with complete heart block and torsades de pointes [3].

Adverse Effects

Cardiovascular:
Serious disturbances of cardiac rhythm such as ventricular asystole or fibrillation are more common with IV administration of procainamide than with IM administration. If evidence of

QRS widening of more than 25% or marked prolongation of the Q-T interval occurs, concern for overdosage is appropriate, and interruption of the infusion is advisable if a 50% increase occurs[7].
Transient but severe lowering of blood pressure has been reported, particularly during IV administration [7].

Black Box Warning

The use of procainamide hydrochloride as well as other antiarrhythmic agents should be reserved for patients with life-threatening ventricular arrhythmias. The prolonged administration of procainamide often leads to the development of a positive ANA test, with or without symptoms of a lupus erythematosus-like syndrome. Agranulocytosis, bone marrow depression, neutropenia, hypoplastic anemia, and thrombocytopenia in patients receiving procainamide hydrochloride have been reported (in adults), some of which were fatal. Discontinue procainamide if hematologic disorders are identified [3].

Solution Compatibility

D_5W (conflicting data), 0.45% NaCl, and NS.

Solution Incompatibility

D_5W (conflicting data) [9][10].

Terminal Injection Site Compatibility

Amiodarone, dobutamine, famotidine, flumazenil, heparin, hydrocortisone, lidocaine, netilmicin, ranitidine, remifentanil, and sodium nitroprusside.

Terminal Injection Site Incompatibility

Esmolol, milrinone, and phenytoin.

Monitoring

Continuous monitoring of the EKG, blood pressure and heart rate [1][3]. Measure procainamide and N-acetyl procainamide (NAPA) concentrations at 2, 12, and 24 hours after starting the loading dose infusion [4].

Therapeutic concentrations:

Procainamide: 4 to 10 mcg/mL, NAPA 6 to 20 mcg/mL [4][5][6].

Sum of procainamide and NAPA: 10 to 30 mcg/mL [4].

Increasing frequency of toxicity associated with procainamide levels greater than 10 mcg/mL [3].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Procainamide is a class IA antiarrhythmic agent that increases the effective refractory period of the atria and the ventricles of the heart. Onset of action occurs within minutes of starting the loading dose. Half-life is approximately 5 hours in the term neonate, and longer in preterms. Metabolized primarily (60%) in the liver to N-acetylprocainamide (NAPA), an active metabolite. The rate of acetylation is primarily genetically determined in adults and children. Preterm neonates have a higher NAPA:procainamide ratio than term infants presumably due to delayed excretion of NAPA. Renal function is a significant determinant of procainamide clearance [4][3][8].

ABOUT

Special Considerations/Preparation

Available in 10-mL vials providing 100 mg/mL or 2-mL vials providing 500 mg/mL. Store at room temperature. **Do not freeze.**

Dilute initial bolus dose to a final concentration of 20 mg/mL prior to administration. Maintenance infusion should be diluted to 2 to 4 mg/mL in compatible solution before administration [3].

Propranolol

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Hypertension and Tachyarrhythmias
Starting oral dose: 0.25 to 1 mg/kg/dose orally every 6 hours [1][2][3].
Increase as needed to **maximum of 3.5 mg/kg/dose orally every 6 hours**.

Starting IV dose: 0.01 mg/kg/dose IV every 6 hours over 10 minutes.
Increase as needed to **maximum of 0.15 mg/kg/dose IV every 6 hours**.
Effective dosage requirements will vary significantly.

Infantile Hemangiomas
Not approved in infants younger than 5 weeks[4].
Optimal maintenance dose, timing, and duration have not been established.[5].
Week 1: 0.6 mg/kg/dose orally twice daily, at least 9 hours apart [4].
Week 2: 1.1 mg/kg/dose orally twice daily [4].
Week 3: 1.7 mg/kg/dose orally twice daily for 6 months. Adjust the dose periodically as the child's weight increases. May re-initiate if hemangiomas recur [4]. *2.3 to 3.4 mg/kg/day was recommended (guideline dosing)*[6].
Continuation of therapy until full involution of the lesion has occurred or until 1 year of age has been recommended [7], typically continue until at least 8 to 12 months of age (treatment duration of 3 to 12 months) [5]. Recurrences have been reported with early discontinuation of therapy [8]. Tapering periods have ranged from 2 weeks to 1 month [9][10][11][12][13].
Dose adjustment: In infants with PHACE syndrome (posterior fossa defects, hemangiomas, cerebrovascular arterial anomalies, cardiovascular anomalies, and eye anomalies), especially in the presence of neurovascular anomalies, slowly titrate dose, use the lowest effective dose, and administer in 3 divided doses. Lower doses may also be necessary in patients with progressive IH ulceration while receiving therapy and in patients who experience adverse effects (e.g. sleep disturbances) [6].

Uses

Tachyarrhythmias and **hypertension**. Preferred therapy for **supraventricular tachycardia** if associated with Wolff-Parkinson-White syndrome. Palliation of **tetralogy of Fallot** and **hypertrophic obstructive cardiomyopathy**. Adjunctive treatment of **neonatal thyrotoxicosis**.
In 287 infants (median age, 17 days), oral propranolol 3.6 +/- 1 mg/kg/day divided every 6 hours controlled 67.3% of arrhythmias (reentrant arrhythmias or atrial tachycardia) in a retrospective study. The average dose for propranolol monotherapy, which was successful, at discharge was 4 mg/kg/day. One patient discontinued propranolol due to an adverse event

(bradycardia) [1].

Infantile hemangiomas (IH): The first-line agent for IH requiring systemic treatment is oral propranolol. Oral prednisoLONE or predniSONE are alternatives when propranolol is contraindicated or when there is a lack of response to propranolol. For bulky IH during proliferation or when critical anatomic locations are involved, then intralesional injection of triamcinolone and/or betamethasone is recommended. For thin and/or superficial IH, topical timolol is an option [6]. The strength of evidence is high for the effectiveness of propranolol for reducing IH lesion size; although, the optimal dosage, timing, and duration of propranolol therapy, as well as the potential for long-term harm, is not known [15]. The FDA-approved age for initiation of propranolol is 5 weeks to 5 months based on a randomized, double-blind study (n=460) [4] and in retrospectives studies (n=124), the age of initiation of treatment was usually older than 1 month of age; however, neonates have been treated with propranolol for hemangiomas [16][17]. The mean age of treatment initiation was 9.4 months (2 to 54 months) in a retrospective study (n=99) [16].
In a randomized study (n=34), propranolol 2 mg/kg/day was noninferior to prednisoLONE 2 mg/kg/day for the proportion of patients with IH (mean age, 3.3 months; range, 0.3 to 8.2 months) who achieved clinical response at 16 weeks (95.65% vs 91.94%, respectively). There was also no significant difference between propranolol and prednisoLONE for volume reduction (55.87% vs 46.52%) or median time to progression stop or regression (12 vs 11 days) [18].
In a randomized, double-blind study (n=460), 60% of patients treated with 3 mg/kg/day for 6 months of oral propranolol compared with 4% of placebo-treated patients experienced complete or nearly complete resolution of IH after 24 weeks of treatment (p less than 0.001). Re-treatment with propranolol from week 24 to week 96 was necessary in 10% of propranolol-treated patients [19]. In a multi-center retrospective study (n=980), 25.3% of the infants experienced rebound growth of IH after a mean duration of 11.4 months of propranolol [20].
The use of surgical therapy was reduced but not eliminated in propranolol treated pediatric patients with nasal IH in a retrospective study (n=58) [17].

Pediatric FDA Approved Indications: Indicated for the treatment of proliferating infantile hemangioma requiring systemic therapy. Initiate treatment at age 5 weeks to 5 months. Safety and effectiveness for infantile hemangioma have not been established in pediatric patients older than 1 year [4].

Administration

Intravenous: Administer 1 mg/mL at a rate not to exceed 1 mg per minute [14]. Consider diluting to 0.1 mg/mL.
Oral: Administer during or right after a feeding, skip the dose if the child is not eating or is vomiting [4]..

MEDICATION SAFETY

Contraindications/Precautions

Contraindications

- Blood pressure less than 50/30 mmHg [4]
- History of bronchial asthma or bronchospasm [4]
- Cardiogenic shock [23]
- Decompensated heart failure [4][23]
- Heart rate less than 80 beats/minute [4]
- Pheochromocytoma [4]
- Premature infants with corrected age less than 5 weeks [4]
- Second or third degree heart block [4] (if no pacemaker is present) [23]
- Sick sinus syndrome (if no pacemaker is present) [23]
- Sinus bradycardia (if no pacemaker is present) [23]
- Infants weighing less than 2 kg [4]

Precautions

Cardiovascular: Cardiac failure and cardiogenic shock may occur; dose adjustment or discontinuation may be required [23].

Cardiovascular: Patients with Wolff-Parkinson-White syndrome may be at risk for severe bradycardia; monitoring recommended and dose reduction or discontinuation may be required [23].

Cardiovascular: Patients with compensated congestive heart failure may experience worsening myocardial contractility depression and more severe failure [4].

Cardiovascular: Patients with overt congestive heart failure may experience worsening of clinical symptoms [23]

Cardiovascular: Patients with occult coronary artery disease are at increased risk of angina or myocardial infarction with abrupt drug discontinuation [23].

Cardiovascular: Bradycardia [4], including sinus pause, heart block, and cardiac arrest, have been reported [23]; monitoring recommended and dose reduction or discontinuation may be required [4][23].

Cardiovascular: New or worsening hypotension may occur in children with administration of oral solution; monitoring recommended and discontinuation may be necessary [4].

Concomitant use: Non-dihydropyridine calcium channel blockers (eg, verapamil, diltiazem), digoxin, or clonidine increase the risk of severe bradycardia, including sinus pause, heart block, and cardiac arrest; monitoring recommended and dose reduction or discontinuation may be required [23].

Concomitant use: Abrupt withdrawal of concomitant clonidine therapy may exaggerate clonidine withdrawal syndrome and increase risk of rebound hypertension [23].

Dermatologic: Skin reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, erythema multiforme, and urticaria have been reported [24].

Endocrine and metabolic: Patients with thyrotoxicosis may experience masked clinical signs of hyperthyroidism; abrupt withdrawal may precipitate thyroid storm [23].

Endocrine and metabolic: Hypoglycemia may occur at any time during therapy, especially during fasting or when glucose demands are increased; withhold dose during these times and discontinue if suspected. Concomitant corticosteroids may also increase risk of hypoglycemia [25].

Endocrine and metabolic: Use caution in patients with diabetes mellitus since masking of hypoglycemia symptoms may occur [23].

Hepatic: Hepatic impairment increases risk of drug toxicity; monitoring and dose adjustment may be required [23].
Immunologic: Hypersensitivity reactions, including anaphylaxis, have been reported; epinephrine may be less effective in beta-blocker-treated patients [4] therefore consider other therapies, including IV fluids and glucagon, if anaphylaxis occurs [23].
Musculoskeletal: Exacerbation of myopathy and myotonia have been reported in patients with skeletal muscle disease [26].
Renal: Renal impairment increases risk of drug toxicity; monitoring and dose adjustment may be required [23].
Respiratory: Use not recommended in patients with bronchospastic lung disease [24].
Respiratory: Bronchospasm may occur with oral solution administration; therapy interruption may be necessary in patients with lower respiratory tract infection [4].
Special populations: Caution advised in patients with PHACE (posterior fossa abnormalities, hemangioma, arterial lesions, cardiac abnormalities or aortic coarctation, and abnormalities of the eye) syndrome with severe cerebrovascular anomalies due to increased risk of stroke; evaluate prior to therapy [4].
Surgery: Use caution during anesthesia or major surgery as decreased ability of heart to respond to reflex adrenergic stimuli may occur; routine discontinuation of long-term therapy prior to surgery not recommended [23]

Adverse Effects

Adverse effects are related to beta-receptor blockade. Significant reductions in myocardial function and hypotension resulting in cardiac compromise have been reported in association with beta-blockers, especially during IV administration in infants. May cause AV block. Bradycardia, fatigue, headache, dizziness, somnolence, diarrhea, anorexia, insomnia, personality changes, and depression are the most common adverse effects reported in children. Bronchospasm may occur. Case reports of hypoglycemia occurring in children after therapeutic doses, in absence of diabetes [14][21][22][27][28][29].

Infantile hemangioma: The most common (10% or more) adverse events in infants treated for infantile hemangioma were sleep disorders, aggravated respiratory tract infections, peripheral coldness, agitation, diarrhea, somnolence, nightmare, irritability, decreased appetite, abdominal pain, and vomiting [4].
Asymptomatic and symptomatic hypoglycemia, requiring hospitalization, have been reported in infants receiving propranolol for the treatment of infantile hemangioma. Infants less than 3 months of age are at increased risk [30][31][12]. Hypoglycemia including hypoglycemic seizures were typically associated with poor oral intake or concomitant infection [32]. Concomitant corticosteroids increase the risk of hypoglycemia [4].
Within 2 hours the effect on heart rate and blood pressure were evident [32].

Solution Compatibility

D_5W and NS.

Terminal Injection Site Compatibility

Alteplase, dobutamine, heparin, hydrocortisone succinate, linezolid, milrinone, morphine, potassium chloride, and propofol.

Monitoring

Continuous ECG monitoring should be done during acute treatment of arrhythmias and during IV therapy. Measure systemic blood pressure frequently. Monitor vital signs and measure blood glucose during initiation of treatment and after dosage changes. Assess for increased airway resistance [4][12][14][21][22].
When treating infantile hemangiomas, monitor heart rate and blood pressure for 2 hours after the first or increasing dose [4]. Perform a complete history and physical examination with particular attention to cardiac and pulmonary systems. Electrocardiography may be considered, particularly in younger infants, those with a low heart rate, and those at risk of congenital heart disease (by examination or family history) [5]. Before treating large facial infantile hemangioma with propranolol, assess for potential arteriopathy associated with PHACE syndrome [4].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action: Potential molecular mechanisms of action for propranolol in the treatment of infantile hemangioma include vasoconstriction (reduction of blood flow to the hemangioma), inhibition of angiogenesis (decreased expression of vascular endothelial growth factor and inhibition of tubulogenesis of endothelial cells), and induction of apoptosis in endothelial cells [33].
Propranolol is the most widely used nonselective β-adrenergic-receptor blocking agent. Peak serum concentration is reached approximately 2 hours after an oral dose. Propranolol undergoes significant first-pass hepatic metabolism, resulting in 30% to 40% bioavailability. Protein binding is 70% in neonates. Serum half-life is prolonged in patients with liver disease. Elimination is by renal excretion of metabolites.

ABOUT

Special Considerations/Preparation

Availability
Oral: 4 mg/mL and 8 mg/mL oral solution (contains 0.6% alcohol) and a 4.28 mg/mL propranolol hydrochloride (3.75 mg/mL propranolol) alcohol-, paraben-, and sugar-free solution (Hemangeol™); do not freeze. Do not shake Hemangeol™ before use and discard the bottle 2 months after opening. Oral tablets available in 10-, 20-, 40-, 60-, and 80-mg strengths.
Injectable: 1 mg/mL vials
Make a 0.1 mg/mL dilution by adding 1 vial (1 mg/mL) to 9 mL preservative-free normal saline. **Protect from light.** Store at room temperature.

Extemporaneous Oral Compound
Propranolol 2 mg/mL and 5 mg/mL suspension are stable for 120 days when stored in amber plastic bottles at 25°C or 4°C [34]

- **2 mg/mL**
- In a mortar, triturate 20 propranolol 40-mg tablets into a fine powder
- Add Ora-Blend SF incrementally for a total of 400 mL
- **5 mg/mL**
- In a mortar, triturate 50 propranolol 40-mg tablets into a fine powder
- Add Ora-Blend SF incrementally for a total volume of 400 mL

Protamine

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Intravenous
Heparin-induced bleeding
Time since last heparin dose in minutes and protamine dose:
Less than 30 minutes: 1 mg per 100 units heparin received [1].
30 to 60 minutes: 0.5 to 0.75 mg per 100 units heparin received [1].
60 to 120 minutes: 0.375 to 0.5 mg per 100 units heparin received [1].
Greater than 120 minutes: 0.25 to 0.375 mg per 100 units heparin received [1].

Maximum dose: 50 mg

Low Molecular Weight Heparin-induced bleeding
Dalteparin: Protamine 1 mg IV for every 100 anti-Xa international units of dalteparin; if APTT (measured 2 to 4 hours after the first infusion) remains prolonged, a second infusion of protamine sulfate 0.5 mg per 100 anti-Xa international units of dalteparin may be administered; maximum neutralization of the anti-Factor Xa activity is about 60% to 75% [2].
Enoxaparin: Protamine 1 mg IV for every 1 mg of enoxaparin administered in the previous 8 hours; if more than 8 hours has elapsed since the last dose of enoxaparin was administered, or if APTT (measured 2 to 4 hours after the first infusion) remains prolonged, a second infusion of protamine 0.5 mg per 1 mg of enoxaparin may be administered; if more than 12 hours has elapsed since enoxaparin administration, protamine sulfate administration may not be necessary; the maximum neutralization of the anti-Factor Xa activity is about 60% [3].
Tinzaparin: Protamine 1 mg IV for every 100 anti-Xa international units of tinzaparin; if APTT (measured 2 to 4 hours after the first infusion) remains prolonged, a second infusion of protamine 0.5 mg per 100 anti-Xa international units of tinzaparin may be administered; the maximum neutralization of the anti-Factor Xa activity is about 60% [4].

Uses

For the treatment of **heparin-induced bleeding** [1][5].

For the treatment of **low molecular weight heparin-induced bleeding**. Although the safety effectiveness of protamine sulfate among pediatric patients has not been approved by the US Food and Drug Administration, the American College of Chest Physicians (AACP) Evidence Based Clinical Practice Guidelines state that for treatment of low molecular weight heparin (LMWH)-induced bleeding, protamine sulfate will neutralize anti-IIa activity and partially neutralize anti-Xa activity. Protamine sulfate dosing is dependent on the dose of the LMWH administered and repeated doses may be required [1].

Administration

Administer intravenously. Recommended to be given undiluted, but if necessary, may further dilute in D_5W or NS. Infusion rate of a 10 mg/mL solution (undiluted) should not exceed 5 mg/min [1][5].

MEDICATION SAFETY

Adverse Effects

Excessive doses can cause serious bleeding problems. Hypotension, bradycardia, dyspnea, and transitory flushing have been reported in adults [5].

Black Box Warning

Hypotension, cardiovascular collapse, pulmonary edema, pulmonary vasoconstriction, and pulmonary hypertension may occur [5][6]. Cases of life-threatening pulmonary hypertension and severe hemorrhagic pulmonary edema have been reported in infants after protamine administration [7]. Risk factors for severe protamine adverse reactions include high doses, rapid administration, repeated doses, previous exposure to protamine or protamine-containing drugs (eg, NPH insulin, protamine zinc insulin, and certain beta blockers), known hypersensitivity reactions to fish, severe left ventricular dysfunction, and abnormal preoperative pulmonary hemodynamics. Vasopressors and resuscitation equipment should be available. Should not be used for bleeding occurring without prior heparin use [5].

Solution Compatibility

D_5W and NS.

Terminal Injection Site Compatibility

Cimetidine and ranitidine.

Terminal Injection Site Incompatibility

Most cephalosporins and penicillins.

Monitoring

Monitor vital signs, clotting functions, and blood pressure continuously. Observe for bleeding.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Anticoagulant when given alone. Combines ionically with heparin to form a stable complex devoid of anticoagulant activity. Rapid action after IV use (5 minutes) [5].

ABOUT

Special Considerations/Preparation

Available as a 10-mg/mL concentration (preservative-free) in 5- and 25-mL vials. Store at room temperature Can be diluted in D_5W or NS if necessary [5].

Protein C Concentrate (Human)

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Prevention and Treatment of Venous Thrombosis and Purpura Fulminans associated with Protein C Deficiency:
Acute Episode/Short-Term Prophylaxis:
Initial dose: 100 to 120 international units/kg IV, followed by 60 to 80 international units/kg IV every 6 hours for next 3 doses [1].
Maintenance dose: 45 to 60 international units/kg IV every 6 or 12 hours [1].

Dose regimen should be adjusted to maintain a target peak protein C activity of 100%. After resolution of acute episode, maintain trough protein C activity level above 25% for duration of treatment. Continue treatment until desired anticoagulation is achieved [1].

Long-Term Prophylaxis: 45 to 60 international units/kg IV every 12 hours. Maintain trough protein C activity level above 25% [1].

Uses

Treatment of patients with severe congenital protein C deficiency for the prevention and treatment of venous thrombosis and purpura fulminans. Also indicated as a replacement therapy [1][2][3][4].
For patients beginning warfarin therapy (vitamin K antagonist therapy), continue protein C until stable anticoagulation is achieved. Begin warfarin therapy at a low dose and titrate up to desired anticoagulation.

Administration

Administer solution at a concentration of 100 international units/mL by IV infusion at a **maximum rate of 0.2 mL/kg/minute**[1].

MEDICATION SAFETY

Adverse Effects

Patients receiving protein C and initiating oral anticoagulant therapy are at increased risk for warfarin-induced skin necrosis. Most serious and common adverse events reported were hypersensitivity or allergic reactions and lightheadedness. Made from human blood. Bleeding episodes were reported in clinical studies. Product contains small amount of heparin. Patients with renal impairment may experience sodium overload (contains greater than 200 mg of sodium in maximum daily dose) [1].

Monitoring

Measure plasma level of protein C before and during treatment. During acute thrombotic events, measure protein C activity immediately before the next dose until the patient is stabilized; dose regimen should be adjusted to maintain a target peak protein C activity of 100% (1 international unit/mL). After stabilization, maintain trough protein C activity level above 25% (0.25 international units/mL). Monitor coagulation parameters (including platelet count) during therapy. Closely monitor patients with renal impairment for sodium overload (contains greater than 200 mg of sodium in maximum daily dose) [1][3].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Protein C, a precursor of a vitamin K-dependent anticoagulant glycoprotein, is activated by the thrombin/thrombomodulin-complex on the endothelial cell surface resulting in subsequent potent anticoagulant effects. Once activated, protein C inactivates the activated forms of factors V and VIII with subsequent reduction in thrombin formation. Other effects include profibrinolytic effects. The pharmacokinetic profile in children has not been studied extensively. One pharmacokinetic analysis determined a half-life of 4.2 to 8.3 hours and a recovery of about 44% after infusion in children. Limited data also suggests a faster clearance and larger volume of distribution in young children which may lead to significantly reduced C_{max} and therefore, reduced systemic exposure compared to older subjects [1][3].

ABOUT

Special Considerations/Preparation

Available in single-dose vials that contain nominally 500 (blue color bar) or 1000 (green color bar) international units human protein C. Vials should be brought to room temperature and reconstituted with 5 mL and 10 mL of sterile water for injection, respectively, to provide a concentration of 100 international units/mL. Should be used within 3 hours of reconstitution. A filter needle should be used to withdraw dose from vial. When reconstituted, contains the

following excipients: human albumin 8 mg/mL, trisodium citrate dihydrate 4.4 mg/mL, and sodium chloride 8.8 mg/mL. **Store unopened vials at 2 to 8 degrees C and protect from light. Avoid freezing**[1].

Pyridoxine

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Pyridoxine-Dependent Seizures
Initial diagnostic dose: 50 to 100 mg IV push, or IM [1][2][3].

Maintenance dose: 50 to 100 mg orally every 24 hours [3]. High doses may be required during periods of intercurrent illness.

Uses

Diagnosis and treatment of pyridoxine-dependent seizures. The test dose of pyridoxine to confirm diagnosis of PDS is not well established. The consensus is that diagnosis of PDS is confirmed when high doses of pyridoxine achieve complete seizure control that has been resistant to traditional antiepileptics. Pyridoxine and antiepileptics are then withdrawn, followed by a reoccurrence of clinical seizures that are, again, successfully treated with pyridoxine monotherapy [4][5][1][2][3].

MEDICATION SAFETY

Adverse Effects

There have been reports of prolonged depression of neurologic and respiratory function, as well as depression of cerebral electrical activity when given either orally or IV. Cardiorespiratory monitoring is recommended and ventilator support may be necessary with initial administration of pyridoxine. When given IV, there have been reports of bradycardia, apnea, and hypotension. Pyridoxine injection contains aluminum that may be toxic with prolonged IV administration in patients with renal impairment or in premature infants (immature kidney function) [6][8][3].

Solution Incompatibility

Alkaline solutions

Terminal Injection Site Incompatibility

Iron salts and oxidizing agents. No data are currently available on heparin and potassium chloride.

Monitoring

When possible, initial administration of pyridoxine should be accompanied by EEG monitoring. Monitor for cardiorespiratory depression [6][5][1]. Monitor for signs of peripheral neuropathy with long-term use [3]. A pyridoxine level than less 20 nanomoles/L is indicative of deficiency [7]

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Pyridoxine is a coenzyme in amino acid and carbohydrate metabolism required for the conversion of tryptophan to both niacin and neurotransmitter serotonin and conversion of dopa to dopamine. It is also required for the synthesis of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). Pyridoxine-dependent seizures are a result of defective binding of pyridoxine in the formation of GABA. They typically present in the neonatal period or early infancy; however, seizures can occur for the first time at up to 3 years of age. In addition to seizures, presentation may include hypothermia, jitteriness, encephalopathy, abdominal distension, and vomiting. Administration of pharmacologic doses of pyridoxine will correct this GABA deficiency [7][6][1][9].

ABOUT

Special Considerations/Preparation

Injection: 100 mg/mL (1 mL in 2-mL vial) [8]

Oral: 40 mg/mL oral liquid [10]. Tablets and capsules available in various strengths (25, 50, 100, 200, 250, and 500 mg).

Extemporaneous Compound
Pyridoxine 1 mg/mL oral solution[11]

- Using a syringe, draw up 1 mL (100 mg) from Pyridoxine 100 mg/mL vial for injection
- Add to prescription bottle

- Add 99 mL of syrup USP/NF (simple syrup)
- Label with "Refrigerate" and an expiration of 30 days

Pyridoxine 25 mg/mL oral suspension[12]
- Dilute pyridoxine hydrochloride 100 mg/mL for injection in Oral Mix or Oral Mix SF
- Stable for 91 days in amber glass bottles, plastic bottles, or oral plastic syringes at 25°C
- Stable for 91 days in amber glass or plastic bottles at 4°C

Pyridoxine 50 mg/mL oral suspension [13]
- Pyridoxine, as an active pharmaceutical ingredient, was compounded with SyrSpend® SF PH4 to make a 50 mg/mL suspension
- Stable for 90 days at refrigeration (2 to 8 degrees C) and room temperature (20 to 25 degrees C)
- Shake suspension for 1 minute before measuring dose

Quinupristin/Dalfopristin

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

7.5 mg/kg/dose every 12 hours by IV infusion.
Administration via a central catheter is recommended.

Uses

Limited to treatment of infections caused by gram positive organisms resistant to other antibiotics, eg, methicillin-resistant *Staph aureus* and vancomycin-resistant *Enterococcus faecium* (not *E faecalis*).

Administration

Give by intermittent IV infusion over 60 minutes at a concentration of 2 mg/mL. A concentration up to 5 mg/mL may be used for central lines. Concentrations less than 1 mg/mL may be used if venous irritation occurs following peripheral administration. Flush peripheral line with D_5W before infusion if other drugs are administered through the same IV line, and after infusion to minimize venous irritation. Infusion through a central line will decrease the risk for venous irritation. **Do not flush with saline or heparin** due to incompatibility [1].

MEDICATION SAFETY

Adverse Effects

Myalgias and arthralgias occur frequently in adults with hepatic or renal failure. Elevations in serum bilirubin and transaminases are common. Diarrhea and rash occur infrequently.

Solution Compatibility

D_5W.

Solution Incompatibility

NS.

Terminal Injection Site Compatibility

Aztreonam, fluconazole, metoclopramide, and potassium chloride.

Monitoring

Periodic measurement of serum bilirubin and transaminases. Assess peripheral IV site for signs of inflammation.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

No data are available for infants. Synercid® is a parenteral antimicrobial agent which consists of two streptogramin antibiotics (quinupristin and dalfopristin in a 30:70 ratio) that inhibit bacterial protein synthesis by binding to separate sites on the bacterial ribosome. Serum half-life of quinupristin in adults ranges from 1 to 3 hours, and of dalfopristin ranges from 5 to 9 hours. Seventy-five percent is excreted via the biliary route.

ABOUT

Special Considerations/Preparation

Synercid® is supplied as a lyophilized powder in single-dose, 10-mL vials containing 500 mg or 600 mg. Store refrigerated. Reconstitute 500-mg and 600-mg vials by adding 5 mL or 6 mL of Sterile Water for Injection or D_5W, respectively, resulting in a concentration of 100 mg/mL. Reconstituted solution should be diluted within 30 minutes. Before administration, dilute with D_5W to a concentration of 2 mg/mL. A concentration up to 5 mg/mL may be used for central lines. Concentrations less than 1 mg/mL may be used if venous irritation occurs following peripheral administration. Diluted solution is stable for 5 hours at room

temperature, or 54 hours if stored under refrigeration. **Do not freeze**.

DOSING/ADMINISTRATION

Dose

Retinopathy of Prematurity, Type I
Intravitreal Route: Studies used intravitreal doses of 0.25 mg/0.025 mL [1][2][3] or 0.3 mg/0.03 mL [4]. Lower intravitreal doses, 0.12 mg/0.02 mL [5] and 0.2 mg/0.02 mL were effective in a pilot study (n=19 infants) [5] and retrospective case series (n=21 infants) [5][6].

Premedication/Postprocedure medication
Anesthesia and broad-spectrum microbicide should be given prior to injection [7].
In infants, eyes were prepared with a topical anesthesia (0.5% proparacaine or 0.5% tetracaine) and ophthalmic antiseptic (5% [2][1][8] or 10% [9] povidone iodine) . After the procedure ophthalmic antibiotic drops were administered for 7 days [4][8].

Uses

Retinopathy of Prematurity (ROP)
Summary: In infants with Type 1 retinopathy of prematurity, one intravitreal ranibizumab injection typically results in initial regression in all treated eyes [4][1][2]. In a prospective randomized trial, recurrence occurred significantly more often with ranibizumab than with laser photocoagulation (LPC) therapy in patients with Zone II, Stages 2 or 3 ROP with plus disease [4]. A large retrospective case series reported a higher rate of recurrence with ranibizumab compared with bevacizumab or LPC but treatment groups differed significantly in relation to baseline characteristics [1]. Vascular abnormalities may persist after primary treatment with ranibizumab [10]. Systemic vascular endothelial growth factor suppression was not sustained with intravitreal doses of 0.12 mg or 0.2 mg in 19 infants [5]. Intravitreal ranibizumab is well tolerated [4][1][2] but long-term systemic effects are unknown for ranibizumab [4][1] and other vascular endothelial growth factor inhibitors [11].

Dose: Ranibizumab intravitreal doses of 0.12 mg/0.02 mL and 0.2 mg/0.02 mL were effective without suppressing plasma vascular endothelial growth factor levels, in a prospective randomized study (n=19 infants). The majority of eyes had posterior zone II, stage 3 with plus disease. The second most common was zone I, stage 3 with plus disease. At 24 weeks, rescue treatment was not needed in 17 of 18 treated eyes (94.4%) with 0.12 mg and 13 of 14 eyes (92.9%) with 0.2 mg. Recurrences severe enough to require retreatment occurred in 2 infants in each group (8 eyes (21.1%)) [5].

•At 44 to 150 weeks postmenstrual age, fluorescein angiograms demonstrated 50% of eyes reached vascularization to zone III, 40% had persistent vascular leakage, and 90% or more showed vascular blunting, vascular dilatation, and/or capillary dropout with intravitreal

ranibizumab 0.15 to 0.2 mg for type 1 ROP including aggressive posterior ROP. At an average of 85 weeks postmenstrual age, 15 of the 16 infants required bilateral laser ablation for delayed vascularization in a retrospective study [10].

•In a prospective, randomized, single center study of 50 Han Chinese infants (100 eyes) with Zone II retinopathy of prematurity (ROP) requiring treatment (ie, Stages 2 or 3 with plus disease), significantly more eyes (52%) developed recurrence after a single dose of intravitreal ranibizumab 0.3 mg compared with laser photocoagulation (LPC) therapy (4%). Recurrence was defined as recurrent plus disease, neovascularization, or reformation of ridge. Initial regression of neovascularization and plus disease occurred within 1 week in all patients who received ranibizumab. All patients who recurred following ranibizumab achieved successful regression following subsequent LPC therapy that was administered at a median of 12.62 weeks later. The one patient (4%) who failed initial LPC subsequently received one injection of ranibizumab, resulting in successful regression. Mean follow-up time was approximately 1 year and long-term systemic safety of ranibizumab was not evaluated [4].

•In a retrospective case series conducted at two Turkish centers of 134 infants (264 eyes), recurrence to Stage 1 or 2 ROP occurred in 50% of the 22 infants treated with intravitreal ranibizumab 0.25 mg, 5.5% of the 55 infants treated with intravitreal bevacizumab 0.625 mg (significant difference compared with ranibizumab), and 1.8% of the 57 infants treated with LPC therapy. Patients were treated according to the indications defined by the Early Treatment for ROP (ETROP) study. At baseline, there were significant differences between groups in postmenstrual age (PMA) at treatment (35.59, 34.75, and 36.03 weeks in the ranibizumab, bevacizumab, and LPC groups, respectively) and the number of patients with Zone II involvement (36.4%, 61.8%, and 87.7%, respectively). In addition, aggressive posterior ROP (APROP) was present at baseline in 40,1%, 27.2%, and 1.8%, respectively. After initial treatment, regression occurred in all patients. Of the 11 patients who had a recurrence after initial ranibizumab, 8 spontaneously regressed, one received subsequent LPC, and two received a second dose of ranibizumab (mean time to retreatment, 8.75 weeks). Of the 3 patients with recurrence after initial bevacizumab, one received subsequent LPC, and two received a second dose of bevacizumab (mean time to retreatment, 14 weeks). The final resolution rate was 100% in the ranibizumab and bevacizumab groups and 98.2% in the LPC group (Stage 4A retinal detachment in one patient). Minor cases of transient subconjunctival hemorrhage occurred in the drug treatment groups but no major ocular complications were reported. Significantly higher rates of myopia (100%) and high myopia (71.4%) in Zone I occurred in the LPC group compared with the ranibizumab (42.9% and 14.3%) and bevacizumab (57.1% and 23.8%) groups but rates for Zone II did not differ significantly between groups. At an adjusted 1.5 years of age, the rate of emmetropia was significantly higher in the ranibizumab (45.5%) and bevacizumab (50.9%) groups compared with the LPC group (16.3%). Long-term systemic safety was not assessed [1].

•A retrospective single center study of 128 infants with Type 1 ROP and 18-month follow-up examinations found recurrence rates of 16.7% (1 of 6 patients) with intravitreal ranibizumab 0.25 mg and 8.3% (1 of 12 patients) with intravitreal bevacizumab 0.625 mg following initial regression within 48 hours in all patients who received either ranibizumab or bevacizumab. Recurrence was defined as recurrent plus or preplus disease or neovascularization, or progression of traction. In a third group of 36 patients who received LPC therapy, initial regression occurred in 1 to 2 weeks except in 5 patients who required retreatment with LPC at 10 days. Differences in the ranibizumab, bevacizumab, and LPC groups at baseline were found in birth weight (840, 841, and 1112 grams, respectively), number of patients with Stage 3 disease (16.7%, 16.7%, and 61.1%, respectively), APROP (83.3%, 83.3%, and 19.4%, respectively), and Zone II disease (66.7%, 83.3%, and 88.9%, respectively). A fourth group of 74 patients with spontaneously regressed ROP was included. The two

patients with recurrence after ranibizumab or bevacizumab therapy achieved successful regression following subsequent LPC therapy. Mean total vascularization time was significantly shorter with ranibizumab (61.8 weeks of PMA) compared with bevacizumab (73 weeks of PMA). Following LPC, one patient experienced exudative retinal detachment and nystagmus in both eyes and one patient had macular ectopia and nystagmus; no ocular complications were noted in other groups other than transient preretinal hemorrhages [2].

Pediatric FDA Approved Indications
Safety and effectiveness have not been established in pediatric patients [7].

Administration

Preparation
Syringe
•Only open the sealed tray under aseptic conditions [7].
•Snap off the syringe cap without turning or twisting [7].
•Remove any air bubbles [7]
Vial
•Under aseptic conditions, withdraw all of the ranibizumab vial contents (0.2 mL) through a 19-gauge x 1.5- inch, 5-micron filter needle attached to a 1-mL Luer lock syringe [7].
•After withdrawal, discard the filter needle [7]
•Do not use the filter needle for intravitreal injection [7]
•Remove any air bubbles [7]

Administration
•In pediatric patients a sterile 30-gauge [2][4][7], 31-gauge [1], or 32-gauge [9] 4-mm needle injected ranibizumab 0.75 mm [10][9] to 1 mm [9] or 1.5 mm [10][2][4][1] posterior to the temporal limbus into the vitreous cavity [10][9].
•To treat the contralateral eye, use a new vial or prefilled syringe and change the sterile field, gloves, drapes, eyelid speculum, filter needle (vial only), and injection needles before administration [7].

MEDICATION SAFETY

Contraindications/Precautions

Contraindications
•Ocular or periocular infections [7].

Precautions
Cardiovascular: Arterial thromboembolic events (nonfatal stroke, nonfatal myocardial infarction, or vascular death) have occurred [7].
Ophthalmic: Endophthalmitis and retinal detachments have been reported; monitor [7].
Ophthalmic: Intraocular pressure increase has been observed prior to injection and within

60 minutes after injection; monitor [7].

Adverse Effects

Ophthalmic Effects

The most commonly reported adverse effects in adult patients were conjunctival hemorrhage, eye pain, vitreous floaters, and increased intraocular pressure [7].
Adverse events suspected to be related to intravitreal ranibizumab were conjuctival hemorrhage, retinal detachment, injection site hemorrhage with the 0.12 mg dose (5 out of 10 infants) and conjunctival hemorrhage, corneal edema, retinal hemorrhage, and retinal vascular disorder with the 0.2 mg dose (4 out of 9 infants). Serious retinal detachment was suspected of to be related to intravitreal ranibizumab 0.12 mg (1 out of 10 infants) [5].
A large avascular area in zone II and zone III were present in 8 eyes (3%) at 24 weeks after intravitreal ranibizumab . These eyes had abnormal vessel shunting and branching on fundus photography [12].
More high myopia was seen in eyes treated with bevacizumab (14.6%) than those treated with ranibizumab (0%) at 1 year of age in a retrospective study (n=37 infants) [3].
Cataract (0.7%) and vitreous and preretinal hemorrhage in 1 eye (0.4%) occurred in a retrospective case series of 145 premature infants of retinopathy of prematurity [12].

Non-ophthalmic Effects

Respiratory failure and hypotension occurred in 1 infant with ROP administered intravitreal ranibizumab 0.2 mg (1 out of 9 infants) [5].

Monitoring

•Monitor the treated eye for increased intraocular pressure with tonometry before and 30 minutes after intravitreal injection [7].
•Assess for perfusion of the optic nerve head immediately after intravitreal injection [7].
•Monitor the treated eye for signs and symptoms of endophthalmitis (redness, sensitivity to light, pain, vision changes) following intravitreal injection [7].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action

Ranibizumab is an inhibitor of the human vascular endothelial growth factor A (VEGF-A). Ranibizumab binds to the receptor binding site of the active forms of VEGF-A, which prevents VEGF-A from interacting with the surface receptors of endothelial cells. This blockage results in reduced endothelial cell proliferation, vascular leakage, and new blood vessel formation

[7].

Cmax: Mean Cmax values of 1.7 +/- 1.1 ng/mL were observed in adults with neovascular age-related macular degeneration following monthly intravitreal ranibizumab injections of 0.5 mg. The predicted serum ranibizumab concentrations in humans are approximately 90,000-fold lower than vitreal concentrations [7].
Half-life: Average vitreous elimination half-life was approximately 9 days based on population pharmacokinetic analysis of patients with neovascular age-related macular degeneration following monthly intravitreal ranibizumab injections of 0.5 mg/eye [7].

ABOUT

Special Considerations/Preparation

Availability: 0.3 mg (6 mg/mL) or 0.5 mg (10 mg/mL) single-use, prefilled syringes and 0.3 (6 mg/mL) or 0.5 mg (10 mg/mL) 2-mL single use vials of ranibizumab [13].
Storage: Store vials and prefilled syringes under refrigeration and in original carton, between 2 and 8 degrees C (36 and 46 degrees F). Protect prefilled syringes form light. Do not freeze [13].

DOSING/ADMINISTRATION

Dose

The marketing and distribution of all prescription and over-the-counter (OTC) ranitidine drugs was discontinued in the US on 4/1/2020 due to the presence of N-Nitrosodimethylamine (NDMA), which may result in exposure to unacceptable levels of this impurity [1].
Oral: 2 mg/kg/dose orally every 8 hours [2][3].
IV
Term: 1.5 mg/kg/dose IV every 8 hours slow push [4].
Preterm:0.5 mg/kg/dose IV every 12 hours slow push [4].
Continuous IV infusion: 0.0625 mg/kg/hour IV maintained pH at or above 4; whereas, 0.031 mg/kg/hr maintained a median pH of 2.65 in 10 preterm neonates [5][6][7]; 0.03 to 0.06 mg/kg/hr was estimated to maintain an average **raNITIdine** concentration above 100 to 200 nanograms/mL in an exploratory, single-dose, pharmacokinetic study in 27 term infants within the first day of life [8].

Extracorporeal membrane oxygenation (ECMO)
2 mg/kg/dose IV every 12 to 24 hours; gastric pH greater than 4 will be maintained for at least 15 hours in neonates on ECMO based on limited data. A continuous infusion [9] (initiated at 0.083 mg/kg/hr; increased in increments of 0.042 mg/kg/hr if gastric pH fell to less than 4) maintained pH greater than 4 in more than 90% of 13 term neonates undergoing ECMO [10].

Uses

Crying and irritability: In otherwise healthy term infants, histamine$_2$ receptor antagonists or proton pump inhibitors should not be used for the treatment of crying and distress [13].

Prevention and treatment of stress ulcers and GI hemorrhage aggravated by gastric acid secretion.
Apnea of prematurity: Reducing gastric acidity or increasing gastric motility for the sole purpose to reduce apnea episodes is not supported by the literature [14].
Gastroesophageal Reflux (GER): The risks associated with acid reducing agents outweighs the benefits in preterm infants for GER. Acid blocking agents should not be used and if used in preterm infants, use sparingly [15]. In otherwise healthy term infants, histamine$_2$ receptor antagonists or proton pump inhibitors should not be used for the treatment of visible regurgitation [13].
Gastroesophageal Reflux Disease (GERD): Proton pump inhibitors (PPIs) are the first-line agents for erosive esophagitis in infants and children with GERD. Histamine$_2$ receptor

antagonists are the second-line agent if PPIs are not available or are contraindicated. A duration of treatment for 4 to 8 weeks for GERD symptoms is recommended. Regularly reassess the need for long-term acid suppression. If no response after 4 to 8 weeks, then re-evaluate for other causes of symptoms. H_2RAs and PPIs are not recommended for extraesophageal symptoms (e.g. cough, wheezing, asthma), unless GERD symptoms are present and/or GERD has been diagnosed [13].
A trial use of PPIs as a diagnostic test for GERD is not recommended in infants or in patients presenting with extraesophageal symptoms. However, in children with typical GERD symptoms, a trial of 4 to 8 weeks with a PPI may be used as a diagnostic test [13].

Administration

IV bolus: May use 1 mg/mL preservative-free solution for injection or dilute in NS to a maximum concentration of 2.5 mg/mL and give over at least 5 minutes **(maximum 4 mL/minute)**[11].
Intermittent IV infusion: Dilute in D_5W or other compatible solution to a concentration of no greater than 0.5 mg/mL and give over 15 to 20 minutes **(maximum 5 to 7 mL/minute)**[11]. A standard concentration of 1 mg/mL may be used [12].
Continuous IV infusion: Dilute in D_5W or other compatible solution to a concentration of 0.5 mg/mL or less [11]. A standard concentration of 1 mg/mL may be used [12].

MEDICATION SAFETY

Contraindications/Precautions

PRECAUTIONS
Hepatic: Use with caution in patients with hepatic dysfunction [16].
Infection: Increased risk of infections (necrotizing enterocolitis, pneumonia, upper respiratory tract infections, sepsis, urinary tract infections, and *Clostridium difficile* infections) in infants and children on H_2 blockers or PPIs demonstrated in case-control studies [13][17].
Special Populations: Avoid in patients with a history of acute porphyria as raNITIdine may precipitate acute porphyric attacks [16].
Special Populations: In phenylketonuric patients, Zantac® 25 EFFERdose® tablets contain phenylalanine 2.81 mg [16].

Adverse Effects

General: RaNITIdine is generally well tolerated by infants, children and adults, and has a low incidence of adverse effects, including rash, headache, fatigue, irritability, dizziness, nausea, constipation, and diarrhea, that are usually mild. Elevations in hepatic enzymes,

leukopenia, and bradycardia have been reported in adults [18][11].

Hematological: Severe thrombocytopenia (8 X 10^9/L) developed in a male infant (gestational age 36 weeks and 5 days; weight 1.8 kg) 48 hours (5 days of age) after starting ranitidine 0.5 mg/kg IV every 6 hours for prophylaxis of stress ulcer and as a potential gastric emptying stimulator. Ranitidine was discontinued on day 6, platelets increased on day 8, then normalized on day 12 [19].

Immunological
The use of H2-blockers in preterm infants has been associated with facilitating *Candida* species colonization [20], and an increased risk for late-onset bacterial and fungal sepsis [21][20].
In a prospective, multicenter, observational study comparing VLBW neonates receiving raNITIdine (n=91) to those not receiving raNITIdine (n=183), neonates receiving raNITIdine had an increased rate of infection (37.4% versus 9.8%; OR 5.5; 95% CI, 2.9 to 10.4), increased risk for NEC (9.8% versus 1.6%; OR 6.6; 95% CI, 1.7 to 25), and increased mortality (9.9% versus 1.6%) [22].
In a retrospective, case-control study, H2-blocker use in VLBW infants was associated with an increased incidence of NEC (OR 1.7; 95% CI, 1.34 to 2.19) [23].

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Acyclovir, acetazolamide, amikacin, aminophylline, ampicillin, atropine, aztreonam, cefazolin, cefepime, cefoxitin, ceftazidime, chloramphenicol, clindamycin, dexamethasone, digoxin, dobutamine, dopamine, enalaprilat, epinephrine, erythromycin lactobionate, fentanyl, fluconazole, flumazenil, furosemide, gentamicin, glycopyrrolate, heparin, insulin, isoproterenol, lidocaine, linezolid, lorazepam, meropenem, metoclopramide, midazolam, milrinone, morphine, nicardipine, nitroprusside, pancuronium bromide, penicillin G, piperacillin, piperacillin/tazobactam, potassium chloride, propofol, protamine, remifentanil, tobramycin, vancomycin, vecuronium, vitamin K_1, and zidovudine.

Terminal Injection Site Incompatibility

Amphotericin B, pentobarbital, and phenobarbital.

Monitoring

Gastric pH may be measured to assess efficacy.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action: Inhibits gastric acid secretion by histamine H_2-receptor antagonism [9].

Tmax: Peak serum concentration occurs 1 to 3 hours after oral administration and is not influenced by food.
Bioavailability is quite variable.
Metabolism: Hepatic biotransformation predominates after oral absorption, with 30% excreted unchanged in the urine. In contrast, 70% of an IV dose is excreted unchanged in the urine.
Half-life: Elimination half-life in neonates is 3 to 7 hours, and is prolonged in preterm infants and patients with renal or hepatic insufficiency.

Pharmacokinetic Studies:
In children 1 day to 12.6 years of age (n=17), the half-life, Vd, and Cl were around 2.4 hours, 2 L/kg, and 11.7 mL/min/kg, respectively. In comparison in children older than 12 years of age (n=6), the half-life, Vd, and Cl were around 1.7 hours, 0.98 L/kg, and 9.89 mL/min/kg, respectively [9].

Extracorporeal membrane oxygenation: The half-life, Vd, and Cl were 6.6 hours, 1.8 L/kg, and 4.3 mL/min/kg, respectively, in 12 neonates on ECMO [9].

ABOUT

Special Considerations/Preparation

The marketing and distribution of all prescription and over-the-counter (OTC) ranitidine drugs was discontinued in the US on 4/1/2020 due to the presence of N-Nitrosodimethylamine (NDMA), which may result in exposure to unacceptable levels of this impurity [1].

DOSING/ADMINISTRATION

Dose

Anthrax; meningitis or disseminated infection and meningitis cannot be ruled out (as part of a triple therapy regimen) [1]
32 up to 38 weeks gestational age
0 to 4 weeks: 5 mg/kg/dose IV every 12 hours
38 weeks or more gestational age
0 to 1 week: 5 mg/kg/dose IV every 12 hours
1 to 4 weeks: 10 mg/kg/dose IV every 12 hours
Duration: 2 to 3 weeks or more until stable. Continue antimicrobial course of prophylaxis (usually oral therapy) for up to 60 days from onset of illness [1].

Anthrax; meningitis ruled out (as part of a combination regimen) [1]
32 weeks or more gestational age: 10 mg/kg/dose IV every 24 hours
Duration: 2 to 3 weeks or more until stable. Continue antimicrobial course of prophylaxis (usually oral therapy) for up to 60 days from onset of illness [1].

Haemophilus influenzae type b disease (invasive); prophylaxis for high-risk contacts: 10 mg/kg per dose orally every 24 hours for 4 days [2].

Meningococcal disease (invasive); prophylaxis for high-risk contacts: 5 mg/kg per dose orally every 12 hours for 2 days [3].

Staphylococcal infections, persistent
Oral: 10 to 20 mg/kg/dose every 24 hours. May administer with feedings.
IV: 5 to 10 mg/kg/dose every 12 hours [4][5][6][7], given via syringe pump.
Do not administer IM or subQ.

Uses

Anthrax[1]:

Systemic Anthrax when meningitis can be ruled out (IV)
Combination IV Therapy

- **Preferred:** Ciprofloxacin. *Alternatives in order of preference: meropenem, levofloxacin, imipenem/cilastatin, or vancomycin. If strains are penicillin-susceptible, then penicillin G (preferred) or ampicillin (alternative).*
- **Plus**
- **Preferred:** Clindamycin. *Alternatives in order of preference: linezolid, doxycycline (not*

for neonates 37 weeks gestation or younger), or rifAMPin.

Systemic Anthrax (meningitis or disseminated infection and meningitis cannot be ruled out) (IV)
Triple IV Therapy

- **Preferred:** Ciprofloxacin. *Alternatives in order of preference: levofloxacin or moxifloxacin*
- **Plus**
- **Preferred:** Meropenem. *Alternatives in order of preference: imipenem/cilastatin or doripenem. If strains are penicillin-susceptible, then penicillin G (preferred) or ampicillin (alternative).*
- **Plus**
- **Preferred:** Linezolid. *Alternatives in order of preference: clindamycin or rifAMPin or as a last resort, chloramphenicol*

H influenzae type b; Prophylaxis

N meningitidis; Prophylaxis

Infective endocarditis The following recommendations are based on a consensus of experts [9]. The full pediatric guidelines can be found here: https://doi.org/10.1161/CIR.0000000000000298.

<table>
<tr><th colspan="3">Initial Empirical Therapy or Culture-Negative Endocarditis*</th></tr>
<tr><td>Unknown Organism</td><td>First-Choice</td><td>Alternative Choice</td></tr>
<tr><td>Native valve (community acquired)</td><td rowspan="2">Ampicillin/sulbactam + gentamicin with or without vancomycin
For prosthetic valve involvement, add rifAMPin</td><td rowspan="2">Vancomycin + gentamicin</td></tr>
<tr><td>"Late" prosthetic valve infection (more than 1 year after surgery)</td></tr>
<tr><td>Nosocomial endocarditis associated with vascular cannulae</td><td rowspan="2">Vancomycin + gentamicin (with or without rifAMPin if prosthetic material present) + cefepime or cefTAZidime</td><td rowspan="2">Unknown</td></tr>
<tr><td>"Early" prosthetic valve endocarditis (1 year or less after surgery)</td></tr>
</table>

* Culture-negative endocarditis (CNE): generally, attempt to culture the infecting organism for at least 48 hours. Severely ill children need immediate treatment. Consider infectious disease consultation for CNE
Baltimore, 2015

Organism Directed Therapy		
Organism	First-Choice	Alternative Choice
Streptococci		
Highly susceptible to penicillin G (MBC 0.1 mcg/mL or less); includes most viridans streptococci, groups A, B, C, G nonenterococcal, group D streptococci (S bovis, S equinus)	Penicillin G or CefTRIAXone	Vancomycin or First-generation cephalosporin or CefTRIAXone
Relatively resistant to penicillin (MBC 0.2 mcg/mL or more); less-susceptible viridans streptococci or enterococci	Penicillin G or Ampicillin + Gentamicin (for first 2 weeks, or entire course for enterococci)	Vancomycin + Gentamicin for enterococci Ampicillin + CefTRIAXone (for aminoglycoside (AMG)-resistant enterococci or AMG-intolerant patient) CefTRIAXone + gentamicin (not for enterococcal endocarditis)
Resistant to penicillin	Consult an infectious disease specialist.	---
Staphylococci (S aureus or coagulase-negative staphylococci) †		
Penicillin G susceptible (1 mcg/mL or less) (rare)	Penicillin G	Oxacillin or Nafcillin or First-generation cephalosporin

		or Vancomycin
Penicillin G resistant (0.1 mcg/mL)	Oxacillin or Nafcillin with or without Gentamicin	Vancomycin (for those highly allergic to beta-lactam antibiotics) or First-generation cephalosporin
Oxacillin (MRSA) resistant (4 mcg/mL)	Vancomycin	Daptomycin for right-sided endocarditis, maybe for left-sided
Vancomycin resistant or intolerant	Daptomycin	Unknown
	†When prosthetic material present add riFAMpin + gentamicin (for first 2 weeks) for all staphylococci	
Gram-negative enteric bacilli	CefTAZidime or Cefepime or Cefotaxime or CefTRIAXone Plus gentamicin (or tobramycin or amikacin, depending on susceptibility)	Broad-spectrum penicillin Plus gentamicin (or tobramycin or amikacin)
HACEK group	CefTRIAXone or Cefotaxime or Ampicillin-sulbactam	Ampicillin (when susceptible) Plus aminoglycoside
KEY: AMG = aminoglycosides; HACEK = Haemophilus species, Aggregatibacter species, Cardiobacterium hominis, Eikenella corrodens, and Kingella species; MBC = minimum bactericidal concentration, MRSA = methicillin-resistant Staphylococcus aureus (includes resistance to oxacillin, nafcillin, and cephalosporins)		
Baltimore, 2015		

Staphylococcal infections (persistent) in combination with vancomycin or aminoglycosides [4][5][6][7].

Administration

Intravenous: Administer by intermittent IV infusion over 30 minutes to 3 hours at a **concentration not exceeding 6 mg/mL**. Avoid extravasation during infusion [8].

MEDICATION SAFETY

Contraindications/Precautions

Contraindications

• Concomitant use in patients receiving rilpivirine or elvitegravir/cobicistat [17], atazanavir, darunavir, fosamprenavir, saquinavir (unboosted or ritonavir-boosted), or tipranavir; lurasidone; and concomitant use with praziquantel or within 4 weeks prior to praziquantel use (may restart rifampin 1 day after end of praziquantel treatment) [18][19].
• Hypersensitivity to rifampin, any component of the product, or any of the rifamycins [20][21]

Precautions

Administration: Doses greater than 600 mg once or twice weekly; increased risk of serious adverse effects, including flu syndrome, hematopoietic reactions, cutaneous, gastrointestinal, and hepatic reactions, shortness of breath, shock, anaphylaxis, and renal failure [20][22]
Concomitant use: Concomitant use of cefazolin and rifampin in patients at increased risk for bleeding, avoid use; prolongation of prothrombin time may occur and lead to severe, life-threatening or fatal, vitamin K-dependent coagulation disorder. If no other option available, close monitoring required [11][23]
Concomitant use: Use with etravirine, nevirapine, or any protease inhibitor (boosted or unboosted) is not recommended [17]
Concomitant use: Use with maraviroc is not recommended; if clinically warranted, dose adjustments required [17]
Dermatologic: Local irritation and inflammation due to extravascular infiltration has been observed [22]
Dermatologic: Severe cutaneous adverse reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and acute generalized exanthematous pustulosis, have been reported; discontinue if symptoms or signs develop [24][22]
Endocrine and metabolic: Diabetes mellitus; diabetes management may be more difficult [20][22]
Hematologic: Coagulation disorders that are vitamin K-dependent may occur; monitoring recommended in patients at risk of vitamin K deficiency (eg, chronic liver disease, poor nutritional status, on prolonged antibacterial drugs or anticoagulants) and consider discontinuation if abnormal coagulation tests and/or bleeding occurs [11][23]
Hematologic: Cases of thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura and hemolytic uremia syndrome, sometimes fatal, have been reported; discontinuation required and further evaluate unexplained thrombocytopenia and

anemia [20]
Hepatic: Hepatotoxicity of hepatocellular, cholestatic, and mixed patterns have been reported with severity ranging from asymptomatic elevations in liver enzymes, isolated jaundice/hyperbilirubinemia, symptomatic self-limited hepatitis to fulminant liver failure and death. Severe hepatic dysfunction, including fatalities, have been reported in patients with liver dysfunction and concomitant hepatotoxic agents; monitoring is recommended and discontinuation may be necessary [14][15]
Immunologic: Systemic hypersensitivity reactions, including fever, rash, urticaria, angioedema, hypotension, acute bronchospasm, conjunctivitis, thrombocytopenia, neutropenia, elevated liver transaminases or flu-like syndrome, have been reported; monitoring recommended and discontinuation and supportive therapy my be necessary [20][21]
Immunologic: Drug Reaction with Eosinophilia and Systematic Symptoms (DRESS) syndrome has been reported and can be severe or fatal; monitoring recommended and discontinuation required [20][21]
Paradoxical drug reaction: Paradoxical drug reactions have been reported and are often transient; if signs and symptoms occur, consider paradoxical drug reaction in the differential diagnosis, monitor, and treat accordingly [25][26]
Renal: Renal hypersensitivity reactions have been reported upon resuming therapy after intentional or accidental interruption of daily regimen [24][22]
Respiratory: Pulmonary toxicity manifesting as interstitial lung disease has been reported and can be fatal; discontinuation of treatment may be required [27][28].

Adverse Effects

May cause yellow/orange/red/brown discoloration of sweat, urine, tears, sputum, or teeth [29]. Extravasation may cause local irritation and inflammation. **RifAMPin** in a potent inducer of several cytochrome P450 enzymes. If administered concomitantly, the following drugs may have decreased pharmacologic effects due to increased metabolism: aminophylline, amiodarone, cimetidine, corticosteroids, digoxin, enalapril, fluconazole, midazolam, morphine, phenobarbital, phenytoin, propranolol, and zidovudine.

Solution Compatibility

D_5W and NS; both depend on concentration.

Terminal Injection Site Compatibility

RifAMPin diluted to 8.33 mg/mL:
Vancomycin (40 mg/mL).
RifAMPin diluted to 6 mg/mL:
Amiodarone (12.5 mg/mL), amoxicillin/clavulanate (10/2 mg/mL), bumetanide (0.5 mg/mL),

midazolam (0.1 mg/mL), pantoprazole (8 mg/mL), and vancomycin (40 mg/mL).

Terminal Injection Site Incompatibility

Diltiazem and tramadol.

Monitoring

Therapeutic Laboratory Monitoring

Pulmonary TB: Obtain acid-fast bacilli (AFB) smear and culture from sputum at least monthly until 2 consecutive culture specimens are negative. In patients with positive AFB smears upon diagnosis, obtain follow-up smears more frequently (eg, every 2 weeks until two consecutive specimens are negative) [10].

Therapeutic Physical Monitoring

Pulmonary TB: Perform chest x-rays after 2 to 3 months of treatment in patients with negative initial cultures and at end of treatment. In patients with positive cultures at diagnosis, repeat chest x-rays after 2 months of treatment and at completion of treatment are useful but not required. [10].

Toxic Laboratory Monitoring

•Monitor liver function tests, especially ALT and AST levels, prior to starting therapy; continue follow-up monitoring every 2 to 4 weeks during therapy in patients with impaired liver function or receiving other hepatotoxic drugs [8].
•Evaluate a bilirubin level, serum creatinine level, and a CBC panel (including a platelet count) prior to starting therapy and continue follow-up monitoring in patients who have laboratory abnormalities. Pediatric patients do not require baseline testing unless there is a known or suspected complicating condition [8].
•Monitor coagulation tests (prothrombin time and other coagulation tests) in patients at risk of vitamin K deficiency (eg, those with chronic liver disease, poor nutritional status, on prolonged antibacterial drugs or anticoagulants) [11].
•If concomitant use of rifampin and cefazolin cannot be avoided in patients who have an increased risk of bleeding, closely monitor prothrombin time and other coagulation tests as clinically indicated [11].

Toxic Physical Monitoring

•Monitor for signs or symptoms of hypersensitivity reactions (eg, fever, rash, urticaria, angioedema, hypotension, acute bronchospasm, conjunctivitis, thrombocytopenia, neutropenia, elevated liver transaminases, or flulike syndrome) [12][13].
•Monitor for symptoms and clinical signs of liver injury, especially with prolonged use or concomitant use of other hepatotoxic agents [14][15].
•Cytochrome P450 inducer which may decrease serum levels of certain drugs; monitor for possible drug interactions [16]

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action: RifAMPin is a semisynthetic antibiotic with a wide spectrum of antibacterial activity against staphylococci, most streptococci, *H influenzae*, *Neisseria* species, *Legionella*, *Listeria*, some *Bacteroides* species, Mycobacterium tuberculosis, and certain atypical mycobacterium. Enterococci and aerobic gram-negative bacilli are generally resistant. Not used as monotherapy because resistance may develop during therapy. Inhibits transcription of DNA to RNA by binding to the beta subunit of bacterial RNA-polymerase [30].
AUC, multiple dose, 10 to 20 mg/kg/day IV; 22 to 41 weeks gestational age: 105 mg x hr/L for postnatal age 7 days or less; 78 mg x hr/L for postnatal age older than 7 days [19]
Cmax, multiple dose, 12 mg/kg/day IV; postnatal age 7 days or younger: 8.4 mg/L based on PK modeling [19]
Cmax, multiple dose, 14 mg/kg/day IV; postnatal age older than 8 to 90 days: 9.6 mg/L based on PK modeling [19]
Absorption: Well absorbed orally.
Metabolism: Rapidly deacetylated to desacetylrifampin (active metabolite) and undergoes enterohepatic circulation.
Excretion: Nearly all of the **rifAMPin** excreted into the bile is deacetylated within 6 hours.
Clearance: 0.09 L/kg/hr for postnatal age 7 days or less; 0.23 L/kg/hr for postnatal age older than 7 days; doses were 10 to 20 mg/kg/day IV [19]
Half-life: Serum half-life ranges from 1 to 3 hours.

ABOUT

Special Considerations/Preparation

Injection
Availability: Lyophilized powder for injection in 600-mg vials.
Reconstitution: Reconstitute with 10 mL of sterile water for injection to make a final concentration of 60 mg/mL. Reconstituted solution is stable for 24 hours at room temperature.
Dilution: Further dilution is required; maximum concentration for infusion is 6 mg/mL. Dilutions are stable at room temperature for 24 hours when prepared in normal saline and 4 hours when prepared in D_5W [8].

Oral
Available in 150-mg and 300-mg capsules for oral use.

Extemporaneous compounding
RifAMPin 10 mg/mL oral suspension
A **rifAMPin** 10 mg/mL oral suspension can be prepared by using 4 **rifAMPin** 300-mg or 8 **rifAMPin** 150-mg capsules. The contents of the capsules should be crushed into a fine

powder, and a sufficient quantity of any one of four syrups (Syrup, NF, Simple syrup (Humco™), fruit flavored syrup (Syrpalta®, Emerson), raspberry syrup (Humco™)) should be added to bring the volume to 120 mL. This mixture should be labeled "shake well" and is stable for 4 weeks at room or refrigerated temperature [8].

RifAMPin 25 mg/mL suspension

RifAMPin 25 mg/mL suspension is stable for 28 days when stored at room temperature or refrigerated (microbial growth was not studied). To prepare 120 mL of **rifAMPin** 25 mg/mL [31]:

- Empty ten 300 mg capsules OR twenty 150 mg capsules into a mortar.
- Add 20 mL of vehicle (choice of 1:1 Ora-Sweet/Ora-Plus, 1:1 Ora-Sweet SF/Ora-Plus, OR cherry syrup) to the powder and mix until a uniform paste has formed.
- Continue to add vehicle in geometric portions until almost to volume; mix thoroughly after each addition.
- Add the contents of the mortar to a prescription bottle; using vehicle, rinse mortar for any leftover preparation and add to bottle.
- Add sufficient amount of vehicle to a final volume of 120 mL.
- Label bottle with "Shake Well Before Use" and "Protect from light".

Rocuronium

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Time to maximum block for an intubating dose was shortest in infants (28 days up to 3 months) and longest in neonates (birth to younger than 28 days); duration of clinical relaxation following an intubating dose is shortest in children (older than 2 years up to 11 years) and longest in infants[1].
Routine Tracheal Intubation: Initial, 0.6 mg/kg/dose IV; a lower dose of 0.45 mg/kg may be used depending on anesthetic technique and patient age. Must be accompanied by adequate anesthesia or sedation [1].
Routine Tracheal Intubation; Sevoflurane Induction: 0.45 mg/kg and 0.6 mg/kg IV [1][2] produce excellent to good intubating conditions within 75 seconds [1].
Routine Tracheal Intubation; Halothane Induction: 0.6 mg/kg IV [1][3] produce excellent to good intubating conditions within 60 seconds [1].

Skeletal Muscle Relaxation - Maintenance
General Anesthesia; Adjunct to Sevoflurane Induction/Isoflurane and Nitrous Oxide
Bolus dosing: 0.15 mg/kg IV at reappearance of T3 [1].
Continuous infusion: 7 to 10 mcg/kg/minute IV at reappearance of T2 [1][4] with the lowest dose requirement for neonates and the highest dose requirement for children older than 2 years up to 11 years [1].

Uses

Rocuronium 0.45 mg/kg or 0.6 mg/kg IV under isoflurane anesthesia in newborns (N=20) achieved good to excellent intubation conditions in most patients within 60 seconds in a randomized study; a few patients experienced poor conditions with respect to position and movement of vocal cords. Recovery of neuromuscular blockade for 0.45 mg/kg and 0.6 mg/kg, respectively, were 56.4 minutes and 100.8 minutes for T_1 = 75% of baseline and 62.3 minutes and 94.8 minutes for train-of-four ratio of 0.7 [2].

Pediatric FDA Approved Indications
Adjunct to general anesthesia to facilitate routine tracheal intubation, and to provide skeletal muscle relaxation during surgery or mechanical ventilation [1].
Not recommended for rapid sequence intubation in pediatric patients [1]

Administration

•Must be accompanied by adequate analgesia and/or sedation [1].
•Administer IV push over 5 to 10 seconds. Available as a 10 mg/mL solution. May also give as continuous IV infusion in compatible diluent at a concentration up to 5 mg/mL [1].
•Do not mix with alkaline solutions (eg, barbiturate solutions) in the same syringe or administer simultaneously during IV infusion through the same needle [1].

MEDICATION SAFETY

Contraindications/Precautions

Administration: Confirm proper selection of injected product and avoid confusion with other injectable solutions in the critical care setting as administration results in paralysis, which may lead to respiratory arrest and death; progression may be more likely in individuals whom administration is unintended [1].
Administration: Must be accompanied by adequate anesthesia or sedation [1]
Administration: If extravasation occurs, immediately terminate the infusion and restart in another vein [1]
Cardiovascular: An increased circulatory delayed time, which may occur with cardiovascular disease, may delay onset time [1].
Cardiovascular: QT interval prolongation may occur with concomitant use of general anesthetics in pediatric patients [1].
Concomitant use: Do not mix with alkaline solutions (eg, barbiturate solutions) in the same syringe or administer simultaneously during IV infusion through the same needle [1].
Endocrine and metabolic: Malignant hyperthermia may occur [1].
Endocrine and metabolic: Acid-base or electrolyte abnormalities may potentiate or cause resistance to neuromuscular blockade [1].
Immunologic: Severe, life-threatening, and fatal anaphylactic reactions have been reported; caution advised in patients with previous anaphylactic reactions to other neuromuscular blocking agents due to potential for cross-reactivity [1].
Musculoskeletal: Skeletal muscle weakness may occur while weaning from a ventilator after chronic administration in the ICU; continuous monitoring recommended [5].
Musculoskeletal: Myopathy has been reported after long-term administration of other nondepolarizing neuromuscular blocking agents in the ICU as monotherapy or when combined with corticosteroids; when combined with a corticosteroid, limit period of use of neuromuscular blocker and use in settings where benefits outweigh risks [1].
Musculoskeletal: Myasthenia gravis or myasthenic (Eaton-Lambert) syndrome; monitoring recommended due to risk of profound neuromuscular blocking effects [5]
Neurologic: Residual paralysis after extubation may occur. Extubate only after sufficient recovery from neuromuscular blockade [1].
Neurologic: Prolonged paralysis may occur while weaning from a ventilator after chronic administration in the ICU; continuous monitoring recommended [1].
Neurologic: Potentiation of, or resistance to neuromuscular blockade may occur in cachectic or debilitated patients, those with neuromuscular diseases, or carcinomatosis, or with concomitant inhalation anesthetics (eg, enflurane, isoflurane), antibiotics, magnesium salts, lithium, local anesthetics, procainamide, or quinidine; initial dosage adjustment may be required [1].
Neurologic: Resistance to neuromuscular blocking agents can occur with an increased risk

in patients with burns, disuse atrophy, denervation, direct muscle trauma, cerebral palsy, or chronic exposure to anticonvulsants (eg, carbamazepine, phenytoin) or nondepolarizing agents; higher infusion rates may be required [1].
Respiratory: Increased pulmonary vascular resistance may occur; increased risk with underlying pulmonary hypertension or valvular heart disease [1].
Tolerance: Tolerance may develop with chronic administration in the ICU; continuous monitoring recommended [5].

Adverse Effects

The use of rocuronium in infants has only been studied in patients under halothane anesthesia. The overall analysis of ECG data in pediatric patients indicates that the concomitant use of rocuronium with general anesthetic agents can prolong the QTc interval. Most pediatric patients anesthetized with halothane who did not receive atropine for induction experienced a transient increase (30% or greater) in heart rate after intubation, whereas only 1 of 19 infants anesthetized with halothane and fentanyl who received atropine for induction experienced this magnitude of change. Aminoglycosides, vancomycin, and hypermagnesemia may enhance neuromuscular blockade. Propofol has no effect. Phenytoin may diminish neuromuscular blockade. Respiratory and metabolic acidosis prolong the recovery time, respiratory alkalosis shortens it. Rocuronium may be associated with increased pulmonary vascular resistance, so caution is appropriate in patients with pulmonary hypertension. Extravasations cause local tissue irritation. The package insert statement that rocuronium is not recommended for rapid sequence intubations in pediatric patients is due to the lack of studies.

Solution Compatibility

D_5W, Lactated Ringer's, and NS.

Terminal Injection Site Compatibility

Milrinone.

Terminal Injection Site Incompatibility

Micafungin.

Monitoring

Assess vital signs frequently and blood pressure continuously if possible.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Rocuronium is an amino steroid nondepolarizing neuromuscular blocking agent that is an analog of vecuronium with 10% to 15% of its potency. It has a rapid to intermediate onset depending on dose and intermediate duration. It acts by competing for cholinergic receptors at the motor end-plate. This action is antagonized by acetylcholinesterase inhibitors, such as neostigmine and edrophonium. Plasma levels of rocuronium follow a three compartment open model following intravenous administration. The rapid distribution half-life is 1 to 2 minutes and the slower distribution half-life is 14 to 18 minutes. Onset of clinical effect usually occurs within 2 minutes and the duration ranges from 20 minutes to 2 hours. Larger doses (0.9 to 1.2 mg/kg) lead to more rapid onset and longer duration of clinical effect. It can have differential effects on various muscle groups (eg, laryngeal vs adductor pollicis vs diaphragm). The onset of laryngeal adductor paralysis is significantly slower with rocuronium compared with succinylcholine. Despite this difference, rocuronium has the fastest onset of any currently available nondepolarizing muscle relaxant. Average half-life in newborns is 1.1 hours. Rocuronium is approximately 30% protein bound, and is primarily excreted by the liver. There are no known metabolites.

ABOUT

Special Considerations/Preparation

Zemuron® for intravenous injection is available in 5 mL and 10 mL multiple-dose vials containing 10 mg/mL. Each mL contains 10 mg rocuronium bromide and 2 mg sodium acetate. The solution is clear, colorless to yellow/orange, and is adjusted to isotonicity with sodium chloride and to a pH of 4 with acetic acid and/or sodium hydroxide.
Storage: Store refrigerated, 2 to 8 degrees C (36 to 46 degrees F). DO NOT FREEZE. Upon removal from refrigeration to room temperature storage conditions (25 degrees C/77 degrees F), use within 60 days. Use opened vials within 30 days.
To prepare a 1 mg/mL solution, dilute 1 mL of the 10 mg/mL solution up to a final volume of 10 mL with NS. Dilution stable for 24 hours. **Do not mix with alkaline solutions**[1].

DOSING/ADMINISTRATION

Dose

Persistent Pulmonary Hypertension, adjunct

Retinal vascularization must be established before sildenafil is used in extremely preterm infants [1].

IV: loading dose of 0.4 mg/kg over 3 hours, followed by a continuous infusion of 1.6 mg/kg/day (0.067 mg/kg/hour). These data are based on a dose-escalation trial (n=36) and not an efficacy trial [2].

Oral: 0.5 to 1 mg/kg/dose orally 3 times daily [1].
Pharmacokinetics of sildenafil in neonates are highly variable [3]. Careful dose titration while monitoring oxygenation and blood pressure is required.

Uses

Persistent pulmonary hypertension (PPHN), adjunct: The Food and Drug Administration recommends against the use, particularly chronic use, of sildenafil in children due to an observation of increased mortality with increased doses in a long-term, pediatric, clinical trial. However, there may be situations when benefit outweighs risk [5]. In neonates, pulmonary hypertension is often associated with vascular and parenchymal lung disease, necessitating a diagnostic and therapeutic approach distinct from that in older children and adults. In the subset of patients with bronchopulmonary dysplasia (BPD), treating hypoxia, aspiration, and structural airway disease, as well as optimizing respiratory support, is recommended before initiating drug therapy. Oral therapy with either a phosphodiesterase type 5 inhibitor (PDE5i; sildenafil or tadalafil) or endothelin receptor antagonist (ERA; bosentan or ambrisentan) is recommended in children with lower risk PAH. Oral therapy in combination with an inhaled prostacyclin may also be considered in lower risk PAH. The combination of a PDE5i or ERA with epoprostenol IV or treprostinil IV/subQ may be considered in those patients with higher risk PAH [6].
Adjunctive sildenafil may be used in infants with PPHN who are refractory to inhaled nitric oxide, particularly when the oxygenation index is greater than 25 [1]. Use limited to treatment of patients with PPHN refractory to inhaled nitric oxide (iNO) and other conventional therapies, those who are persistently unable to be weaned off of inhaled nitric oxide, or in situations where nitric oxide and high frequency ventilation are not available. According to an intervention review of the use of sildenafil in neonates with PPHN, sildenafil was associated with a significant reduction in mortality with a number need to treat to benefit of 3. All studies included in the review were in resource-limited settings [7]. In a prospective, randomized trial (n=65), oral sildenafil was more effective than magnesium

sulfate in a setting without iNO or high frequency ventilation based on time to adequate effect, duration of mechanical ventilation, and use of inotropic support [8].
Sildenafil has been reported to improve pulmonary blood flow in patients with severe Ebstein's anomaly [9].
A retrospective study (n=7) reported reductions in pulmonary hypertension, and improved respiratory status and oxygenation in neonates with congenital diaphragmatic hernia (CDH) with pulmonary hypertension refractory to inhaled nitric oxide [10].

Administration

Available as 0.8 mg/mL IV solution [4]. Infuse the loading dose over 3 hours [2].

MEDICATION SAFETY

Contraindications/Precautions

Contraindications
Concurrent regular or intermittent use of organic nitrates in any form [4]
Concomitant use with HIV protease inhibitors or elvitegravir/cobicistat/tenofovir/emtricitabine (when used for pulmonary arterial hypertension) [11]
Concomitant use with riociguat [4] or any other guanylate cyclase stimulator [12]

Precautions
An increased mortality with increased doses in a long-term, pediatric, clinical trial has been observed [5].
Cardiovascular: Decreases in blood pressure may occur ; use caution in patients on other antihypertensives, with resting hypotension (BP less than 90/50 mmHg), fluid depletion , left ventricular outflow obstruction (eg, aortic stenosis or idiopathic hypertrophic subaortic stenosis) or severely impaired autonomic control of blood pressure ; monitoring recommended in patients receiving concomitant antihypertensive therapy [4]
Concomitant use: Concurrent use with other phosphodiesterase 5 inhibitors is not recommended [4].
Hematologic: Bleeding events, including epistaxis, have been reported [4].
Respiratory: Use not recommended, especially chronic use, in pediatric patients with pulmonary arterial hypertension due to a dose-related increased risk of mortality [4].
Respiratory: Vaso-occlusive crises requiring hospitalization have been reported in patients with pulmonary hypertension secondary to sickle cell anemia [4].
Respiratory: Not recommended in patients with pulmonary veno-occlusive disease [4].
Ophthalmic: Non-arteritic anterior ischemic optic neuropathy (NAION) has been reported ; increased risk with previous NAION "crowded" optic disc and in patients with other underlying anatomic or vascular risk factors. Immediate medical attention is advised in the event of sudden loss of vision in one or both eyes during treatment with sildenafil [4]..
Ophthalmic: Use of Revatio(R) is not recommended [4]
Otic: Sudden decrease or loss of hearing may occur; prompt medical attention is advised

[4].
Reproductive: Priapism has been reported; increased risk in patients with anatomical deformation of the penis (eg, angulation, cavernosal fibrosis, or Peyronie disease) or conditions that predispose to priapism (eg, sickle cell anemia, multiple myeloma, or leukemia). Painful or prolonged erections (greater than 4 hours) require immediate treatment [4].

Adverse Effects

Use in neonates should be restricted and considered experimental. Data in neonates remain limited. The most concerning short-term adverse effects are worsening oxygenation and systemic hypotension [2]. There is one case report of bleeding after circumcision in a neonate receiving chronic therapy [13]. Use with caution in infants with sepsis. Sildenafil causes transient impairment of color discrimination in adults, and there is concern that it could increase the risk of severe retinopathy of prematurity if used in extremely premature infants. In a study of neonates receiving sildenafil for at least weeks (n=22), positive ocular findings were reported in 4 patients, none of which were considered drug-related [14]. Sildenafil did not increase the risk of retinopathy of prematurity (odds ratio 1.35 (95% CI, 0.39 to 4.62; p=0.63)) in a case-control study (n=68) of premature infants born before 30 weeks gestation. One infant each in the sildenafil group and control group required laser treatment [15].

Monitoring

Continuous monitoring of blood pressure and oxygenation [2].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action:
Sildenafil citrate is an inhibitor of cGMP specific phosphodiesterase type-5 (PDE5) in smooth muscle, where PDE5 is responsible for degradation of cGMP. Sildenafil citrate increases cGMP within vascular smooth muscle cells resulting in relaxation and vasodilation. In patients with pulmonary hypertension, this leads to vasodilation of the pulmonary vascular bed and, to a lesser degree, vasodilation in the systemic circulation. In patients with erectile dysfunction, sildenafil citrate enhances the effect of nitric oxide (NO) by inhibiting PDE5 in the corpus cavernosum. When sexual stimulation causes local release of NO, inhibition of PDE5 by sildenafil citrate causes increased levels of cGMP resulting in smooth muscle relaxation and inflow of blood to the corpus cavernosum [4].

The pharmacokinetics of a single oral dose of 1.5 mg/kg sildenafil (dissolved in water) administered to 12 children (1.5 to 15 years of age) with pulmonary arterial hypertension were [16]:

- Half-life 2.41 +/- 1.18 hours
- Vd 20.1 +/- 14.5 L
- Total clearance 5.85 +/- 2.81 L/hr
- Tmax 0.92 +/- 0.3 hours
- Cmax 366 +/- 179 ng/mL
- AUC 2061 +/- 638 ngXhr/mL

ABOUT

Special Considerations/Preparation

Oral Revatio® is supplied as 20-mg tablets and a 10 mg/mL oral suspension [4]. Viagra® is supplied as 25-mg, 50-mg, and 100-mg tablets [12].

Revatio® oral suspension must be constituted by the pharmacist prior to dispensing to the patient. To prepare the oral solution, shake the Revatio® bottle to loosen the powder. Remove the cap and add 60 mL of water. Shake the closed bottle for a minimum of 30 seconds. Open the bottle and add an additional 30 mL of water and shake the closed bottle for another 30 seconds. The prepared solution contains sildenafil **10 mg/1 mL**. Once reconstituted, the oral solution should be stored below 30 degrees C (86 degrees F) or in the refrigerator for up to 30 days. Do not freeze [4].

The Revatio® oral suspension is supplied as an off-white powder for constitution, forming a white to off-white grape flavored solution, which when constituted with water as directed contains 10 mg/mL of sildenafil. Available in glass bottles containing approximately 112 mL of solution after constitution; a press-in bottle adaptor and oral syringe are supplied with each bottle. The inactive ingredients of sildenafil oral solution include sorbitol, citric acid anhydrous, sucralose, sodium citrate dihydrate, xanthan gum, titanium dioxide, sodium benzoate, colloidal silicon dioxide anhydrous and grape flavor [4].

Intravenous Revatio® is supplied as a single-use vial containing 10 mg (12.5 mL) of sildenafil, equivalent to 0.8 mg sildenafil per mL. Each mL of solution also contains 50.5 mg dextrose and water for injection [4].

To prepare an **oral 2.5-mg/mL suspension** (150 mL), thoroughly crush fifteen (15) 25-mg tablets into a fine powder and add a 1:1 mixture of Ora-Sweet® and Ora-Plus® or methylcellulose 1% and Simple Syrup, NF to make a final concentration of 2.5 mg/mL. Suspension is stable for 91 days in plastic bottles at 4 and 25 degrees C [17]. This extemporaneous suspension was made using the Viagra® (sildenafil) dosage form.

Simethicone

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Dosage should be weight-based whenever possible, otherwise age should be used for dosing [1]
Gas relief
Oral route
Emulsion/Suspension
Younger than 2 years and less than 11 kg: 20 mg orally as needed, after meals and at bedtime. **MAX 240 mg/day**[2][1]

Uses

Colic: Both placebo and simethicone improved colic symptoms, with no difference between the 2 groups, in a double-blind, randomized, crossover study of 83 full term infants (2 to 8 weeks of age) [3].

Pediatric FDA Approved Indications: This drug has not been found by the US Food and Drug Administration (FDA) to be safe and effective, and the drug product labeling has not been approved by the FDA [1].

Administration

Oral route
Emulsion/Suspension
Shake well prior to use [2][1]
Administer with enclosed syringe only. Do not use dropper, spoon, or other dosing device [1]
Dispense into child's mouth toward inner cheek [2][1]
Dose can be mixed with 1 ounce of cool water, formula, or other suitable liquid [2][1]

ABOUT

Special Considerations/Preparation

Oral route

Emulsion/Suspension
Availability: 20 mg/0.3 mL emulsion or suspension/drops [1]
Storage: Store between 20 and 25 degrees C (68 and 77 degrees F). Do not freeze [2][1].

Sodium Bicarbonate

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Hyperkalemia, with metabolic acidosis (4.2% injection, 0.5 mEq/mL)
1 mEq/kg IV or IO given slowly over 10 to 15 minutes; **Maximum dose 50 mEq**[1]

Metabolic acidosis
Dosage based on base deficit:
HCO_3 needed (mEq) = HCO_3 deficit (mEq/L) x (0.3 x body wt [kg])
Administer half of calculated dose, then assess need for remainder [2].

Resuscitation (routine use not recommended)
1 mEq/kg IV/IO slowly [1].

Uses

Metabolic acidosis: Treatment of normal anion gap metabolic acidosis caused by renal or gastrointestinal losses.

Hyperkalemia, with metabolic acidosis - AAP Guidelines: Sodium bicarbonate is a treatment option for hyperkalemia with concurrent metabolic acidosis for neonates. Only the 0.5 mEq/mL solution should be used in newborns [1].

Cardiac resuscitation: Sodium bicarbonate is not a recommended therapy in neonatal resuscitation guidelines [6]. .

Administration

Intravenous: Administer slow IV push. Rapid IV administration (10 mL/min) of hypertonic sodium bicarbonate may lead to serious consequences (hypernatremia, a decrease in CSF fluid pressure, and possible intracranial hemorrhage) in neonates and children younger than 2 years. **MAX 8 mEq/kg/day**[3]. The preferred concentration for slow IV administration in neonates is the 4.2% strength (0.5 mEq/mL) [3]. Another recommended pediatric concentration for infusions is 0.25 mEq/mL [4].
Do not administer by the endotracheal route [5].

MEDICATION SAFETY

Adverse Effects

Bicarbonate administered during inadequate ventilation increases PCO_2, thereby decreasing pH. Rapid infusion of hypertonic solution is linked to intracranial hemorrhage in neonates and infants. Extravasation may cause local tissue necrosis at IV site. Fluid overload, hypocalcemia, hypokalemia, and hypernatremia may occur. Aggressive therapy may result in metabolic alkalosis (associated with muscle twitching, irritability, and tetany) [2][7][8].

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Acyclovir, amikacin, aminophylline, amphotericin B, atropine, aztreonam, cefepime, cefoxitin, ceftazidime, ceftriaxone, chloramphenicol, cimetidine, clindamycin, dexamethasone, erythromycin lactobionate, esmolol, famotidine, furosemide, heparin, hydrocortisone succinate, ibuprofen lysine, indomethacin, insulin, lidocaine, linezolid, milrinone, morphine, nafcillin, netilmicin, penicillin G, phenobarbital, piperacillin/tazobactam, potassium chloride, propofol, remifentanil, vancomycin, and vitamin K_1.

Terminal Injection Site Incompatibility

Amiodarone, ampicillin, calcium chloride, cefotaxime, dobutamine, dopamine, epinephrine, glycopyrrolate, imipenem/cilastatin, isoproterenol, magnesium sulfate, meropenem, methadone, metoclopramide, midazolam, nicardipine, norepinephrine, oxacillin, phenytoin, and ticarcillin/clavulanate.

Monitoring

Monitor ABGs, acid/base status, and serum calcium and potassium [7].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of Action: When bicarbonate is administered, buffering of hydrogen ions occurs, leading to increased production of carbon dioxide and water. Animal studies of resuscitation demonstrate poor coronary perfusion leads to carbon dioxide accumulation within the myocardium, leading to decreased myocardial contractility[9][7].

Pharmacodynamics
Onset: 15 minutes [1]

ABOUT

Special Considerations/Preparation

Availability: Supplied by many manufacturers in multiple concentrations: 4% (0.48 mEq/mL), 4.2% (0.5 mEq/mL; 1 mOsmol/mL), 5% (0.6 mEq/mL; 1.19 mOsmol/mL), 7.5% (0.9 mEq/mL; 1.79 mOsmol/mL) and 8.4% (1 mEq/mL; 2 mOsmol/mL) [7].
Storage: Store solution at controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F) [7].

Preparation
•Maximum concentration used in neonates is 4.2% (0.5 mEq/mL) [7]
•May dilute with sterile water for injection [7].
•Do not infuse with calcium or phosphate containing solutions; precipitation will occur [7]

Sodium Chloride

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Resuscitation (volume expansion): 10 mL/kg IV of sodium chloride 0.9% over 5 to 10 minutes. Consider a second dose of 10 mL/kg if there is no significant improvement after the first dose. Normal saline (sodium chloride 0.9%) is the recommended volume expander. Lactated Ringer's is an acceptable alternative [1].

Sodium Supplementation
Preterm infants: 3 to 5 mEq/kg/day IV or orally [2][3]
Healthy infants: 2 to 3 mEq/kg/day IV or orally [3]

Uses

Resuscitation: Volume expanders should be considered in neonates with clinically apparent hypovolemia, but should not be used in the absence of evidence of acute blood loss. Normal saline (sodium chloride 0.9%) is the preferred isotonic crystalloid solution, and Lactated Ringer's is an acceptable alternative. In babies with severe fetal anemia, O Rh-negative packed red blood cells should be considered as part of volume expansion [1]. The American Heart Association (AHA) did not review the use of volume expanders in the 2015 Neonatal Resuscitation guidelines; therefore, the 2011 AHA guideline still applies [4]

Sodium supplementation: Sodium chloride significantly increased the velocity of weight gain in preterm infants (gestational age [GA] less than 32 weeks) compared with placebo, especially in infants with GA less than 28 weeks. The velocity of weight gain for the duration of the study in patients that received sodium chloride was 26.64 g/kg/day vs 22.91 g/kg/day with placebo (95% CI, 0.97 to 7.08). In a subgroup analysis of patients with GA less than 28 weeks, the percentage increase from birth weight to 6 weeks was 193% in the sodium chloride group vs 173% in the placebo group (95% CI, 0.99 to 40.85). There were no significant differences in adverse events between groups. Sodium chloride 4 mEq/kg/day was administered every 6 hours for 28 days and could be given IV or orally, depending on patient status [2].

Administration

For resuscitation (volume expansion), give normal saline over 5 to 10 minutes. Consider a longer duration of administration in preterm neonates less than 30 weeks GA [1].

MEDICATION SAFETY

Contraindications/Precautions

Contraindications

Large fluid volumes can decrease cardiac output in hypoxic infants. Avoid rapid administration of volume expanders due to the risk for intracranial hemorrhage. Rapid administration of packed red blood cells may precipitate heart failure [1].

Monitoring

Monitor heart rate, blood pressure.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action: Sodium chloride is a source of water and electrolyte [5][6]. Sodium is the principle cation of extracellular fluid and chloride is the principle anion of extracellular fluid. Sodium content normally determines the volume of extracellular fluid, and important in the regulation of osmolarity, acid-base balance, and the membrane potential of cells [7].

ABOUT

Special Considerations/Preparation

IV Route

Availability: 20 mL, 40 mL, and 100 mL vials [8][9]
Storage: Store at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F) [8][9][10]. Brief exposure up to 40 degrees C (104 degrees F) does not adversely affect the solution [6].

Sodium Glycerophosphate

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Phosphate Supplement:1 to 1.5 mmol/kg/day, individualized to needs of patient [1].

Uses

Phosphate supplementation: After administration of sodium glycerophosphate 1.5 mmol/kg/day, mean increases in plasma phosphorus concentrations were 0.33+/-0.08 mmol/L at 12 hours, 0.72 +/-0.3 mmol/L at 36 hours, and 0.9+/-0.3 mmol/L at 60 hours (p less than 0.0001 for all values) from a baseline of less than 0.5 mmol/L in a retrospective report of very low birthweight neonates with hypophosphatemia receiving parenteral nutrition (n=19; mean gestational age 28+/-3 weeks). All patients had been receiving parenteral nutrition solutions with inorganic calcium and phosphorus salts at the limit of solubility when hypophosphatemia resulted. The switch to sodium glycerophosphate as the sole phosphorus source not only increased the amount of phosphorus that could be administered each day, but also allowed an increase in the amount of calcium infused to 1.5 mmol/kg/day. By 60 hours, all patients had achieved a plasma phosphorus concentration of 1.5 mmol/L or greater [2].

Pediatric FDA Approved Indications
Because of the critical shortage of phosphate injection in the United States market, an alternative imported formulation of Glycophos™ has been made available; however, it is not approved by the US Food and Drug Administration [3].

Administration

Must be diluted before administration. Administer over no less than 8 hours [1].

MEDICATION SAFETY

Contraindications/Precautions

Contraindicated in patients with dehydration, hypernatremia, hyperphosphatemia, severe renal insufficiency, or shock [1].

Product contains 2 mEq/mL of sodium. Use with caution in patients with renal impairment [1].
Barcodes on the Glycophos™ product will not be recognized by scanning systems used in the US and should not be used. The product should be manually input into the system. Alternate procedures should be put in place to assure that the correct drug product is being prepared and administered to the patient [3].

Adverse Effects

No adverse effects of sodium glycerophosphate have been reported [2][1].

Solution Compatibility

Up to 10 mL of Glycophos™ and 10 mmol of calcium (as $CaCl_2$) may be added to 1000 mL of D_5W [1].
Up to 20 mL of Glycophos™ and 20 mmol of calcium (as $CaCl_2$) may be added to 1000 mL of $D_{20}W$ [1].
Up to 60 mL of Glycophos™ and 24 mmol of calcium (as $CaCl_2$) may be added to 1000 mL of $D_{50}W$ [1].
As a reference only (these products are not available in the US), up to 120 mL of Glycophos™ and 48 mmol of calcium (as $CaCl_2$) may be added to the following amino acid solutions (1000 mL) [1]:

- Vamin 14 (Ca 5 mmol/L; pH 5.4 to 5.8; amino acids 8.5%; nitrogen 13.5 g/L)
- Vamin 14 (pH 5.4 to 5.8, amino acids 8.5%; nitrogen 13.5 g/L) electrolyte free
- Vamin 18 (pH 5.4 to 5.8; amino acids 11.4%; nitrogen 18 g/L) electrolyte free
- Vaminolact (pH 5.2; amino acids 6.53%; nitrogen 9.3 g/L)

More complete information on the composition of these products is available [4][5].

Monitoring

Regularly monitor phosphate status [1].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Sodium glycerophosphate is an organic phosphate, which is different from the inorganic phosphate products usually used in the US[3]. Organic phosphates tend to be more compatible with calcium, such that solutions of calcium and phosphate may exist at higher concentrations without precipitation and, at higher pH (greater than 6), organic phosphate is less likely to precipitate [3]. It is used as an IV nutritional supplement when plasma phosphate concentrations are low. Bioavailability is dependant on hydrolysis of the phosphate group from the glycerophosphate molecule, which occurs most efficiently at plasma concentrations of greater than 0.7 mmol/L. Normal serum alkaline phosphatase is capable of hydrolyzing approximately 12 to 15 mmol of sodium glycerophosphate each day. Pharmacokinetic data not available for infants [1].

ABOUT

Special Considerations/Preparation

Glycophos™ (sodium glycerophosphate) is a preservative-free concentrated solution (pH 7.4) containing 2 mEq/mL of sodium and 1 mmol/mL of phosphate in a 20-mL single-dose plastic vial [3]. Do not store above 25 degrees C. Do not freeze. Discard vial after use [1].
Note: Glycophos™ contains **1 mmol/mL** of organic phosphate. Sodium and potassium phosphate products typically used in the US are **3 mmol/mL** of inorganic phosphate [3].

Sodium Nitroprusside

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Usual Dosage
Initial dosage: 0.3 mcg/kg/min as an IV infusion; titrate every few minutes until the desired effect is achieved or [1] up to **MAX 10 mcg/kg/min** , but for no longer than 10 minutes at the maximum rate [2][3] or the shortest duration possible [1].

Heart failure: 0.3 to 4 mcg/kg/minute IV infusion **MAX 6 mcg/kg/min** [4].

Risk of thiocyanate toxicity with prolonged administration (more than 72 hours) [5].

Dose Adjustments
Renal
GFR less than 30 mL/min/1.73m^{2}: Limit mean infusion rate to less than 3 mcg/kg/min [6]
Anuria: Limit the mean infusion rate to 1 mcg/kg/min [6]

Uses

•Acute treatment of hypertensive emergencies.
•Acute afterload reduction in patients with refractory congestive heart failure.

Pediatric FDA Approval: Indicated for immediate reduction of blood pressure in pediatric patients in hypertensive crises. Indicated for induction and maintenance of controlled hypotension in pediatric patients during surgery, to reduce bleeding [6].

Administration

Administer as a continuous IV infusion at a concentration of 50 to 500 mcg/mL (0.05 to 0.5 mg/mL). Use a large vein for IV. Protect infusion from light during administration (not necessary to cover tubing) [6][7]. Some institutions use standard concentrations of 60, 125, 200, 400, 500, and 1000 mcg/mL [8]. Administer by volumetric infusion pump [6].

MEDICATION SAFETY

Contraindications/Precautions

Contraindications

Acute heart failure associated with reduced peripheral vascular resistance [6][3]
Compensatory hypertension (aortic coarctation or arteriovenous shunting) [6][3]
Concomitant sildenafil, tadalafil, vardenafil, or riociguat [6]
Congenital (Leber) optic atrophy [6][3]
Inadequate cerebral circulation or moribund patients (ie, ASA class 5E) coming to emergency surgery [6][3]
Tobacco amblyopia [6][3]

Precautions

Anesthesia: Patient's ability to compensate for anemia and hypovolemia may be diminished; when possible, correct preexisting condition prior to use [6][3]
Hematologic: Methemoglobinemia may occur [6]
Hepatic: Hepatic dysfunction predisposes a patient to cyanide toxicity [6].
Neurologic: Increases in intracranial pressure can occur [6][3]
Thiocyanate toxicity: Can occur and may be life-threatening when levels reach 200 mg/L; monitoring recommended and dose adjustment may be required, especially in patients with renal impairment or anuria. Renal hemodialysis may be used to eliminate thiocyanate if severe toxicity occurs [6]
Special populations: Exercise extreme caution in patients who are especially poor surgical risks (eg, ASA Class 4 and 4E) [3]

Adverse Effects

Severe hypotension and tachycardia. Cyanide toxicity may occur with prolonged treatment (greater than 3 days) and high (greater than 3 mcg/kg per minute) doses. Use with caution in liver and renal failure patients due to possible impairment of the metabolism of cyanide to thiocyanate. Extravasation can cause tissue sloughing and necrosis.

Black Box Warning

•Nitroprusside is not suitable for direct injection; the reconstituted solution must be further diluted in sterile 5% dextrose injection before infusion [3](the Ready-To-Use solution (200 or 500 mcg/mL) may be used without further dilution).
•Nitroprusside can cause precipitous decreases in blood pressure, which may result in irreversible ischemic injuries or death; monitor blood pressure continuously while patient is on therapy [1].
• Except when used briefly or at low (less than 2 mcg/kg/min) infusion rates , sodium nitroprusside gives rise to important quantities of cyanide ion, which can reach toxic, potentially lethal levels. The usual dose rate is 0.5 to 10 mcg/kg/min, but infusion at the maximum dose rate should never last more than 10 minutes. If blood pressure has not been adequately controlled after 10 minutes of infusion at the maximum rate, administration of

sodium nitroprusside should be terminated immediately [3].
•Sodium nitroprusside metabolism produces dose-related cyanide, which can be lethal. A patient's ability to buffer cyanide will be exceeded in less than one hour at the maximum dose rate (10 mcg/kg/min); limit infusions at the maximum rate to as short a duration as possible [1].
•Although acid-bas e balance and venous oxygen concentration should be monitored and may indicate cyanide toxicity, these laboratory tests provide imperfect guidance [3].

Solution Compatibility

D_5W, NS, and LR only.

Terminal Injection Site Compatibility

Caffeine citrate, calcium chloride, cimetidine, dobutamine, dopamine, enalaprilat, epinephrine, esmolol, famotidine, furosemide, heparin, indomethacin, insulin, isoproterenol, lidocaine, magnesium, micafungin, midazolam, milrinone, morphine, nicardipine, nitroglycerin, pancuronium, potassium chloride, procainamide, propofol, prostaglandin E_1, ranitidine, and vecuronium.

Terminal Injection Site Incompatibility

Amiodarone.

Monitoring

Continuous heart rate and intra-arterial blood pressure monitoring is mandatory. Daily measurement of RBC cyanide (should be less than 200 ng/mL) and serum thiocyanate (should be less than 50 mcg/mL) concentrations. Assess frequently for development of metabolic acidosis. Daily assessment of renal and hepatic function. Monitor IV site closely.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Direct-acting nonselective (arterial and venous) vasodilator. Immediately interacts with RBC oxyhemoglobin, dissociating and forming methemoglobin with release of cyanide and nitric

oxide. Rapid onset of action with a serum half-life of 3 to 4 minutes in adults. Further metabolized to thiocyanate in the liver and kidney. Thiocyanate is renally eliminated with a half-life of 4 to 7 days.

ABOUT

Special Considerations/Preparation

Available: Powder for injection in 2-mL single-dose 50-mg vials, 50 mg/2 mL (25 mg/mL) concentrated solution, and ready-to-use 10 mg/50 mL (200 mcg/mL) and 50 mg/100 mL (500 mcg/mL) solution in NS.

Powder for injection: Reconstitute powder for injection with 2 to 3 mL of D_5W or NS. **Do not administer reconstituted drug directly from vial.** Dilute entire vial contents to a final concentration of 50 to 1000 mcg/mL (0.05 to 1 mg/mL) in D_5W or NS. Use within 24 hours of preparation. **Protect from light** with aluminum foil or other opaque material. Blue, green or deep red discoloration indicates nitroprusside inactivation. Slight brownish discoloration is common and not significant.
Ready-to-use (200 mcg/mL and 500 mcg/mL): Protect from light, should be stored in its carton until used. Should be clear colorless to red/brown color. Do not use if solution is blue, green, or bright red [1].

Sodium phenylacetate/Sodium benzoate

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Acute Hyperammonemia - Urea Cycle Disorders
Pending Definitive Diagnosis of Urea Cycle Enzyme Deficiency:
Premedication for loading dose: Ondansetron 0.15 mg/kg IV [1]
Loading dose: Sodium phenylacetate 250 mg/kg and sodium benzoate 250 mg/kg in combination with arginine hydrochloride 600 mg/kg as an IV infusion over 90 to 120 minutes [2][3][4][5].
Maintenance dose: Sodium phenylacetate 250 mg/kg and sodium benzoate 250 mg/kg in combination with arginine hydrochloride 600 mg/kg as an IV infusion over 24 hours [2][3][4][5].
Alternative dose: Sodium phenylacetate 250 mg/kg and sodium benzoate 250 mg/kg IV bolus in combination with arginine hydrochloride 250 to 400 mg/kg IV bolus over 90 to 120 minutes, followed by maintenance infusions of sodium phenylacetate 250 to 500 mg/kg/day and sodium benzoate 250 to 500 mg/kg/day in combination with arginine hydrochloride 250 mg/kg/day. **Maximum dose sodium phenylacetate 12 g/day and sodium benzoate 12 g/day, arginine 12 g/day** [1]

Known CPS, OTC, or NAGS Deficiency:
Premedication for loading dose: Ondansetron 0.15 mg/kg IV **Maximum dose sodium phenylacetate 12 g/day and sodium benzoate 12 g/day, arginine 12 g/day**
Loading dose: Sodium phenylacetate 250 mg/kg and sodium benzoate 250 mg/kg in combination with arginine hydrochloride 200 mg/kg as an IV infusion over 90 to 120 minutes [2][3][4][5].
Maintenance dose: Sodium phenylacetate 250 mg/kg and sodium benzoate 250 mg/kg in combination with arginine hydrochloride 200 mg/kg as an IV infusion over 24 hours [2][3][4][5].
Alternative dose: Sodium phenylacetate 250 mg/kg and sodium benzoate 250 mg/kg IV bolus in combination with arginine hydrochloride 250 mg/kg IV bolus over 90 to 120 minutes, followed by maintenance infusions of sodium phenylacetate 250 to 500 mg/kg/day and sodium benzoate 250 to 500 mg/kg/day in combination with arginine hydrochloride 250 mg/kg/day. **Maximum dose sodium phenylacetate 12 g/day and sodium benzoate 12 g/day, arginine 12 g/day** [1]

Known ASS or ASL Deficiency:
Premedication for loading dose: Ondansetron 0.15 mg/kg IV [1]
Loading dose: Sodium phenylacetate 250 mg/kg and sodium benzoate 250 mg/kg in combination with arginine hydrochloride 600 mg/kg as an IV infusion over 90 to 120 minutes [2][3][4][5].
Maintenance dose: Sodium phenylacetate 250 mg/kg and sodium benzoate 250 mg/kg in combination with arginine hydrochloride 600 mg/kg as an IV infusion over 24 hours [2][3][4][5].
Alternative dose (ASS Deficiency): Sodium phenylacetate 250 mg/kg and sodium

benzoate 250 mg/kg IV bolus in combination with arginine hydrochloride 250 mg/kg IV bolus over 90 to 120 minutes, followed by maintenance infusions of sodium phenylacetate 250 to 500 mg/kg/day and sodium benzoate 250 to 500 mg/kg/day in combination with arginine hydrochloride 250 mg/kg/day. **Maximum dose sodium phenylacetate 12 g/day and sodium benzoate 12 g/day, arginine 12 g/day** [1]
Alternative dose (ASL Deficiency): Sodium phenylacetate 250 mg/kg and sodium benzoate 250 mg/kg IV bolus in combination with arginine hydrochloride 200 to 400 mg/kg IV bolus over 90 to 120 minutes, followed by maintenance infusions of sodium phenylacetate 250 to 500 mg/kg/day and sodium benzoate 250 to 500 mg/kg/day in combination with arginine hydrochloride 200 to 400 mg/kg/day. **Maximum dose sodium phenylacetate 12 g/day and sodium benzoate 12 g/day, arginine 12 g/day** [1]

Repeating the loading dose within 24 hours of the initial loading dose should be considered only for patients with a severe disorder receiving dialysis[5].

CPS = carbamyl phosphate synthetase; OTC = ornithine transcarbamylase; NAGS = N-acetyl glutamate synthase; ASS = argininosuccinic acid synthetase; ASL = argininosuccinic acid lyase

Uses

Adjunctive treatment of acute hyperammonemia in neonates with urea cycle disorders. Arginine hydrochloride should be used concomitantly with sodium phenylacetate/sodium benzoate. Hemodialysis is the primary treatment of acute hyperammonemia during the early management period [6][3][7][4][5]. Caloric supplementation, dietary protein restriction, and other ammonia lowering therapies should also be considered during acute hyperammonemic episodes [6].

Administration

Must be administered through a central line. For loading and maintenance doses, dilute sodium phenylacetate/sodium benzoate and arginine in 25 to 35 mL/kg of $D_{10}W$ prior to administration. Infuse the loading dose over 90 to 120 minutes [6][5].

MEDICATION SAFETY

Contraindications/Precautions

Caution advised for use in patients with congestive heart failure, severe renal impairment, or other clinical conditions involving sodium retention with edema; product contains 30.5 mg of sodium per mL. Extravasation may lead to tissue necrosis; administration through central line

required [6].

Adverse Effects

The most common adverse effects include vomiting (9%), hyperglycemia (7%), and hypokalemia (7%). Vomiting and lethargy can occur with higher than recommended doses. Hypotension seen more frequently in patients 30 days of age and less. Potentially life-threatening toxicity can occur with doses greater than 750 mg/kg per day [6][4].

Solution Compatibility

$D_{10}W$ and arginine hydrochloride 10%.

Monitoring

Measure plasma ammonia levels every hour during dialysis until levels stabilize to less than 200 to 300 micromoles/L. Capillary blood should not be used for monitoring ammonia levels. Monitor blood glucose, electrolytes (especially potassium), and acid-base status closely during the acute phase (eg, every 4 hours). Toxicity due to ammonia scavenging drugs presents as ketoacidosis. An anion gap that is greater than 15 mEq/L or has increased by greater than 6 mEq/L from baseline may indicate drug accumulation. Monitor amino acids daily to assess the effectiveness of citrulline/arginine replacement and glutamine removal. Assess AST and ALT levels [6][4][5]. Evaluate neurological status, Glasgow Coma Scale, respiratory status, CT or MRI or fundoscopic evidence of cerebral edema, and/or of gray matter and white matter damage to assess patient response to treatment. Monitor infusion site closely during infusion for signs of extravasation [6].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

The use of sodium phenylacetate and sodium benzoate provides an alternative pathway for waste nitrogen excretion in patients with urea cycle disorders, attenuating the risk for ammonia- and glutamine-induced neurotoxicity. Phenylacetate is conjugated with glutamine via acetylation to form phenylacetylglutamine. Phenylacetylglutamine is excreted by the kidney and results in removal of 2 moles of waste nitrogen for each mole of phenylacetate administered. Benzoate is conjugated with glycine to form hippurate. Hippurate is excreted by the kidney and results in removal of 1 mole of waste nitrogen for each mole of benzoate

administered [6][7][4].

ABOUT

Special Considerations/Preparation

Sodium phenylacetate/sodium benzoate (Ammunol®) is available as a 10%/10% solution in a single-use glass vial containing 50 mL. Contains 30.5 mg of sodium per mL.

During the admixture process, the Millex® Durapore GV 33 mm Sterile Syringe Filter (0.22 micrometer) provided by the manufacturer must be used when injecting Ammunol® into the 10% dextrose IV bag [6].

Sotalol

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

To minimize the risk of induced arrhythmia, hospitalize patients initiating or re-initiating therapy for at least 3 days or until steady-state drug levels are reached, in a facility that can provide cardiac resuscitation and continuous ECG monitoring. Obtain QT interval and normalize serum potassium and magnesium prior to initiation. Calculate estimated CrCl to determine appropriate dosing interval. Withdraw other antiarrhythmic therapy (for a minimum of 2 to 3 plasma half-lives if possible) prior to initiation[1][2][3][4].
Do not start therapy if the baseline QTc interval is greater than 450 milliseconds (JT greater than 330 milliseconds if QRS is over 100 milliseconds)[1][4][2][3].

Initial dose: 1 mg/kg/dose orally every 12 hours.
Gradually increase as needed every 3 to 5 days until stable rhythm is maintained.
Maximum dose: 4 mg/kg/dose orally every 12 hours.

Uses

Treatment of refractory ventricular and supraventricular tachyarrhythmias.

In adults, sotalol is indicated for the treatment of life-threatening, documented ventricular arrhythmias, such as sustained ventricular tachycardia. Its use in patients with less severe arrhythmias, even if the patients are symptomatic, is generally not recommended. Avoid treatment of patients with asymptomatic ventricular premature contractions [3][2].
In adults, sotalol is indicated for the maintenance of normal sinus rhythm (delay in time to recurrence of atrial fibrillation/atrial flutter (AFIB/AFL)) in patients with symptomatic AFIB/AFL who are currently in sinus rhythm. Because sotalol can cause life-threatening ventricular arrhythmias, reserve its use for patients in whom AFIB/AFL is highly symptomatic. Patients with paroxysmal AFIB that is easily reversed (by Valsalva maneuver, for example) should usually not be given Betapace/Betapace AF [3][2].

MEDICATION SAFETY

Contraindications/Precautions

Contraindications
Bronchial asthma or related bronchospastic conditions [2][3][4][6]
Uncontrolled cardiogenic shock [4] or decompensated heart failure [1][2][3]

Congenital or acquired long QT syndromes [2][3][4][6] or a baseline QT interval greater than 450 milliseconds [4][6] for treatment of atrial fibrillation or flutter [2][3]
For treatment of atrial fibrillation or flutter, the oral liquid [4] and IV formulations [6] are contraindicated with CrCl less than 40 mL/min [4]
Serum potassium less than 4 mEq/L [2][3][4][6]
Sinus bradycardia [2][3][4] (less than 50 beats/min during waking hours) [4], sick sinus syndrome, or second or third degree atrioventricular block without a functioning pacemaker [2][3][4][6]

Precautions
Cardiovascular: Serious and potentially fatal arrhythmias such as sustained ventricular tachycardia/fibrillation (VT/VF) [2][3], primarily consisting of torsade de pointes, have been reported; increased risk associated with higher doses, reduced CrCl, female gender [1], prolonged QT interval, bradycardia, atrial fibrillation with sinus node dysfunction [1], and/or cardiomegaly or congestive heart failure [4], during therapy initiation or dose titration [2][3], and history of sustained VT/VF [1][2][3]; monitoring recommended and dosage adjustment [2][3] or discontinuation may be necessary [1][4].
Cardiovascular: Bradycardia, sinus pause, sinus arrest, or heart block may occur and increase the risk of torsade de pointes [1][2][3]; monitoring recommended [1] with concomitant digoxin therapy [4] or patients receiving concomitant negative chronotropes [1]; dose reduction may be necessary [4].
Cardiovascular: Significant hypotension may occur; monitoring recommended [1][2][3][4]
Cardiovascular: New onset or worsening heart failure may occur [4] during initiation or dose increases; monitoring recommended and discontinuation [1][2][3] or dose reduction may be necessary [4].
Cardiovascular: Careful dose titration recommended in patients with recent myocardial infarction, particularly in the presence of markedly impaired ventricular function [4].
Cardiovascular: Exacerbation of angina pectoris and myocardial infarction may occur with abrupt cessation of beta blocker therapy; monitoring and gradual dosage reduction recommended, especially in patients with ischemic heart disease [2][3].
Concomitant use: Not recommended with drugs that prolong the QT interval [2][3].
Concomitant use: Class I or Class III antiarrhythmics should be discontinued at least 3 half-lives prior to dosing with sotalol [4][6].
Concomitant use: Not recommended with Class Ia antiarrhythmics (eg, disopyramide, quinidine and procainamide) and other Class III drugs (eg, amiodarone) [4][6].
Endocrine and metabolic: Hypokalemia or hypomagnesemia can exaggerate the degree of QT prolongation. Correct imbalances prior to use. Consider acid/base and electrolyte status in patients with severe or prolonged diarrhea or those receiving concomitant diuretics [2][3]; monitoring recommended [4]
Endocrine and metabolic: Hyperglycemia may worsen and signs of hypoglycemia may be masked (eg, tachycardia) in patients with diabetes mellitus [2][3]; monitoring recommended [4]
Endocrine and metabolic: Exacerbation of hyperthyroidism, including thyroid storm, may occur upon abrupt withdrawal of beta blocker therapy in patients with thyroid disease. Avoid abrupt withdrawal. Additionally, beta blockade may mask signs of hyperthyroidism [2][3].
Immunologic: Beta-blocker therapy may cause patients with a history of an anaphylactic reaction to a variety of allergens to have a more severe allergic reaction on repeated challenge and to be unresponsive to usual doses of epinephrine [2][3]
Respiratory: Not recommended in patients with bronchospastic diseases. If use is required, dose adjustment is recommended [2][3].

Surgery: Chronic beta-blocker therapy should not be routinely withdrawn prior to major surgery and anesthesia due to the impaired ability of the heart to respond to reflex adrenergic stimuli may augment risks of general anesthesia and surgical procedures [2][3].
Withdrawal: Abrupt withdrawal may result in exacerbation of angina, arrhythmias, myocardial infarction, and unmasking coronary artery disease; taper dose [4][6].

Adverse Effects

Proarrhythmic effects occur in 10% of pediatric patients: sinoatrial block, A-V block, torsades de pointes and ventricular ectopic activity. These effects usually occur in the first few days of treatment. Prolongation of the QT interval is dose-dependent. Other adverse effects include fatigue, dyspnea, and hypotension.

Black Box Warning

To minimize the risk of drug-induced arrhythmia, initiate or reinitiate oral sotalol in a facility that can provide cardiac resuscitation and continuous electrocardiographic monitoring. Sotalol can cause life threatening ventricular tachycardia associated with QT interval prolongation. Calculate creatinine clearance to determine appropriate dosing. If the QT interval prolongs to 500 msec or greater, reduce the dose, lengthen the dosing interval, or discontinue the drug [2][3] Do not initiate intravenous sotalol therapy if the baseline QTc is longer than 450 ms [1].

Monitoring

Therapeutic Physical Monitoring
Atrial Fibrillation/Atrial Flutter
• In pediatric patients, carefully assess therapeutic response, especially in children 2 years and younger who can take a longer time to reach steady-state following dosing [5][6]
Ventricular Arrhythmias
• Closely monitor efficacy (arrhythmia control) in patients with renal impairment [7].
• Following the initiation of therapy or an increase in dose, monitor the response to treatment utilizing a suitable method (eg, programmed electrical stimulation (PES) or Holter monitoring) prior to continuing the patient on chronic sotalol therapy [4][7][6].
• In pediatric patients carefully assess therapeutic response, especially in children 2 years and younger who can take a longer time to reach steady-state [7][6].

Toxic Laboratory Monitoring
• Calculate the CrCl prior to the administration of the first sotalol dose. Continuously monitor CrCl calculations for a minimum of 3 days during the initiation or reinitiation of treatment with sotalol. Additionally, monitor renal function regularly during therapy and when converting from IV to oral administration [4][7][5][6].
• Monitor electrolytes (especially potassium and magnesium which may exacerbate

arrhythmias) prior to and during every gradual upward dose titration, especially in patients with severe or prolonged diarrhea, or in patients receiving concomitant diuretics [4][7][5][6].
• Monitor acid-base balance in patients with severe or prolonged diarrhea, or in patients receiving concomitant diuretics [4][7][5][6].

Toxic Physical Monitoring
• Evaluate the QT interval prior to initiation of sotalol therapy and after each dose titration [4][7][5][6]. Continuously monitor ECG for a minimum of 3 days during the initiation or reinitiation of treatment with orally administered sotalol. During continuous ECG monitoring, measure the QT interval during initiation and titration 2 to 4 hours following each oral dose. Measure the QT interval following the completion of each IV sotalol infusion, to guide dose titration, and when converting from IV to oral administration. Patients at risk of serious ventricular arrhythmias, primarily torsade de pointes associated with QT interval prolongation include reduced creatinine clearance, female gender, and larger doses. Additionally, monitor the QT interval in all patients regularly during therapy. Carefully monitor QT interval in patients with renal impairment since a longer duration of dosing is required to reach steady-state [7][5][6].
• In pediatric patients, closely monitor QT interval and heart rate and carefully assess tolerability, especially in children 2 years and younger who can take a longer time to reach steady-state [4][7][5][6].
• Monitor cardiac rhythm prior to and during every gradual upward dose titration, and especially in patients with renal impairment [4][7].
• Monitor blood pressure in patients with marginal cardiac compensation [4].
• When discontinuing chronically administered sotalol therapy carefully monitor patients, especially in patients with ischemic heart disease [4][7][5][6].
• Monitor for exacerbation of angina pectoris, arrhythmias, and myocardial infarction when discontinuing chronically administered therapy, especially in patients with ischemic heart disease [4][7][5][6].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action: Sotalol hydrochloride is an antiarrhythmic agent with beta-adrenoreceptor blocking (Vaughan Williams Class II) and cardiac action potential duration prolongation (Vaughan Williams Class III) properties. Class III antiarrhythmic effects are seen at higher doses than those needed to achieve beta blockade. Sotalol is not cardioselective and does not possess partial agonist or membrane stabilization properties [4][8][9]

Therapeutic Drug Concentration
AUC
Oral, multiple-dose (steady-state): Within 2 to 3 days [1]
Oral, single- and multiple-dose, children with BSA less than 0.33 m(2): AUC 59% higher compared with larger children [4][9]
Time to peak concentration, oral, children: 2 to 4 hours [4][9]

Absorption
Bioavailability, oral: 90% to 100% [4][9]
Effect of food: Standard meal reduces absorption by approximately 20% [4][9]

Distribution
Protein binding: None [4][9]
Tissue fluids, blood-brain barrier: Poor penetration [4]

Metabolism
Liver: No significant metabolism [4][9][10][11]; (Schnell et al, 1979)

Excretion
Dialyzable: Yes (hemodialysis) [4][12]

Elimination Half-Life
Parent compound, children: 7.4 to 9.5 hours [4][9][13]

ABOUT

Special Considerations/Preparation

Oral solution:
Sotalol 5 mg/mL oral solution is provided in 250 and 480 mL bottles. Store between 20 and 25 degrees C (68 and 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F) [4].

Oral tablets:
Oral formulation supplied in 80-mg, 120-mg, and 160-mg tablets [2][3].
A 5 mg/mL oral suspension may be made as follows: crush 5 (five) 120-mg tablets and add to 120 mL of OraPlus®:OraSweet® (1:1) or 1% methylcellulose:Simple Syrup NF (1:9) in a 6-ounce amber plastic bottle. Shake to adequately suspend. Stable for 90 days at room temperature or refrigerated [9][14].

Spironolactone

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

1 to 3 mg/kg/dose orally every 24 hours.

Uses

Bronchopulmonary dysplasia: Used in combination with other diuretics in the treatment of BPD (situations of increased aldosterone secretion).

Heart failure (HF): Aldosterone antagonist therapy is reasonable for treatment of chronic systolic HF when renal function is normal, or mildly impaired. Spironolactone is the typical agent used as an add-on to ACE inhibitor and beta-blocker therapy when such therapy has not improved ventricular function or reversed ventricular remodeling [2]. Use is not recommended in treatment of HF with preserved ejection fraction [3].
Also may be used cautiously for pulmonary hypertension as supportive care in neonates with signs of right-sided heart failure [4].

Administration

The National Institute for Occupational Safety and Health (NIOSH) recommends the use of single gloves by anyone handling intact tablets or capsules or administering from a unit-dose package [1].
In the preparation of tablets or capsules, including cutting, crushing, or manipulating, or the handling of uncoated tablets, NIOSH recommends the use of double gloves and a protective gown. Prepare in a ventilated control device, if possible. Use respiratory protection if not prepared in a control device. During administration, wear single gloves, and wear eye/face protection if the formulation is hard to swallow or if the patient may resist, vomit, or spit up [1].

MEDICATION SAFETY

Contraindications/Precautions

Contraindicated with concomitant use of eplerenone, and in patients with hyperkalemia, or

Addison disease [5].

Precautions
Endocrine and metabolic: Asymptomatic hyperuricemia may occur and rarely precipitate gout [5].
Endocrine and metabolic: Excessive diuresis may lead to symptomatic dehydration, hypotension, and worsening renal function with an increased risk in salt-depleted patients or those taking ACE inhibitors or angiotensin II receptor blockers [5].
Endocrine and metabolic: Gynecomastia may occur and is usually reversible. Risk increases in a dose-dependent manner [5].
Endocrine and metabolic: Hyperkalemia may occur. Increased risk in patients with impaired renal function or concomitant use of potassium supplementation, potassium-containing salt substitutes, or drugs that increase potassium (eg, ACE inhibitors and angiotensin receptor blockers). Dose adjustment or discontinuation may be necessary [5].
Endocrine and metabolic: Hypomagnesemia, hyponatremia, or hypocalcemia may occur [5].
Endocrine and metabolic: Hypochloremic alkalosis or hyperglycemia may occur [5].
Renal: Worsening renal function may occur with increased risk in patients taking concomitant nephrotoxic drugs (eg aminoglycosides, cisplatin, and NSAIDs) [5].

Adverse Effects

Rashes, vomiting, diarrhea, paresthesias, hyponatremia, hypovolemia. Dose-dependent androgenic effects in females. Gynecomastia in males. Headaches, nausea, and drowsiness. Use with caution in patients with impaired renal function. May cause false positive ELISA screening tests for congenital adrenal hyperplasia [5].

Monitoring

Follow serum potassium closely during long-term therapy. Also, measuring urinary potassium is a useful indicator of effectiveness.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Competitive antagonist of mineralocorticoids (eg, aldosterone). Metabolized to canrenone and 7-a-thiomethylspironolactone, active metabolites with extended elimination half-lives. Decreases excretion of potassium. Highly protein bound. Increases excretion of calcium, magnesium, sodium, and chloride (small effect). Serum half-life with long term use is 13 to 24 hours. Addition of spironolactone to thiazide diuretic therapy in patients with BPD may

yield little, if any, additional benefit.

ABOUT

Special Considerations/Preparation

Suspension
Availability: 25 mg/5mL (5 mg/mL) oral suspension in either a 118- or 473-mL bottle [6].
Storage: Store at a controlled room temperature between 20 and 25 degrees C (68 to 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 to 86 degrees F) [6].

Tablets
Availability: 25-mg, 50-mg, and 100-mg tablets.

Extemporaneous Preparation
•To prepare **25 mg/mL oral suspension**, grind one hundred twenty (120) 25-mg tablets to a fine powder in a mortar. Add 40 mL of vehicle* and mix to a uniform paste. Then add the vehicle in geometric portions and mix after each addition. Transfer contents of the mortar to the calibrated bottle and add enough vehicle to bring the total volume to 120 mL. Protect from light. Shake well. Suspension is stable for 60 days refrigerated or at room temperature (at 5 and 25 degrees C).
*Vehicles: 1:1 mixture of Ora-Sweet® and Oral-Plus®; 1:1 mixture of Ora-Sweet SF® and Oral-Plus®; or cherry syrup (cherry syrup concentrate diluted 1:4 with simple syrup).
•A spironolactone **5 mg/mL suspension**, 480 milliliter, may be prepared using 96 spironolactone 25 milligram tablets (Aldactone(R); Searle), distilled water or glycerin to levigate, Cologel(R) (methylcellulose; Lilly) 160 mL, and a sufficient quantity of a 2:1 simple syrup/cherry syrup mixture to bring the volume to 480 mL. This mixture should be labeled "shake well" and "refrigerate" and is stable for 60 days. A spironolactone/hydrochlorothiazide suspension may be similarly prepared [7].
•A spironolactone **2 mg/mL suspension,** 100 milliliters, may be prepared using spironolactone powder 200 milligrams (Searle), sodium benzoate 100 milligrams, just enough ethanol 10% to form a paste with the powders, and a sufficient quantity of simple syrup to bring the volume to 100 mL. This mixture should be labeled "shake well" and is stable for 160 days at room temperature [8].
•A **2.5- or 5-mg/mL oral suspension** can be made by crushing five or ten 25-mg spironolactone tablets, respectively, and suspending the powder in 50 mL of simple syrup. Suspensions are stable for 1 month refrigerated [9].

The National Institute for Occupational Safety and Health (NIOSH) recommends the use of double gloves and a protective gown by anyone compounding a hazardous oral liquid or any hazardous drug for feeding tube. If possible, prepare in a control device. Respiratory, eye, and face protection are needed if not done in a control device [1].

Succinylcholine

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Skeletal Muscle Relaxation/Paralysis
Intravenous
1 to 2 mg/kg IV immediately prior to intubation [1][2][3][4][5][6][7][8]. Repeat doses of 1 mg/kg up to a maximum total dose of 4 mg/kg have been used if muscle relaxation was not attained by 1 to 3 minutes after administration [4][5].
Must be accompanied by adequate analgesia or sedation [1].

Intramuscular
2 to 4 mg/kg may be given via the IM route only if IV route not accessible [1][3][9].

Uses

Skeletal muscle relaxation/paralysis for neonates requiring rapid sequence intubation or non-emergent endotracheal intubation [2][3][9][11][4][4][12][5][6][7]. Premedication is recommended in neonates for all non-emergent intubations if time permits. Premedication regimens for endotracheal intubation typically include a skeletal muscle relaxant in combination with an analgesic (an opioid) and/or sedative and a vagolytic agent (usually atropine) [2][3][11][8][6]. Use of a muscle relaxant without an analgesic agent is not recommended [3]. Premedication has been shown to decrease the time to successful intubation and decrease the occurrence of adverse effects (ie, increased intracranial pressure, hypertension, decreased heart rate and oxygenation) in neonates [4][12][5][8][7]. Use of succinylcholine has resulted in fewer intubation attempts and more successful intubations compared with no succinylcholine in clinical studies in neonates [11].

Pediatric FDA Approved Indications
Adjunct to general anesthesia, to facilitate tracheal intubation, and to provide skeletal muscle relaxation during surgery or mechanical ventilation [1].

Administration

For IV or IM use only [10]
Medication errors: To reduce risk of accidental administration of neuromuscular blocking agents, which may be fatal, store vial with the cap and ferrule intact and in a manner that minimizes the possibility of selecting the wrong product [10].
Dilute in D5W or NS to a concentration of 1 or 2 mg/mL [10].

Do not administer before unconsciousness has been induced [10]
Administer only in facilities when management of artificial respiration and tracheal intubation for providing adequate ventilation is possible, including the administration of oxygen under positive pressure and the elimination of carbon dioxide; must be prepared to assist or control respiration [10].

MEDICATION SAFETY

Contraindications/Precautions

Contraindications
Acute phase of injury after multiple trauma, major burns, extensive denervation of skeletal muscle, or upper motor neuron injury; may result in severe hyperkalemia and cardiac arrest [13]
Known or suspected genetic susceptibility to malignant hyperthermia [13]
Skeletal muscle myopathies [13]

Precautions
Administration: Should not be administered prior to unconsciousness unless in an emergency situation; no known effect on consciousness or pain threshold [14]. Monitor patients to ensure level of anesthesia is adequate [13].
Administration: Confirm proper selection of intended product and dose prior to administration; paralysis leading to respiratory arrest and death may occur in a patient for whom the product is not intended [13].
Administration: Tachyphylaxis occurs with repeated administration [10].
Cardiovascular: Bradycardia has been reported, potentially progressing to asystole, with an increased risk following repeat exposure; in pediatric patients the incidence and severity is higher and commonly occurs following an initial dose (1.5 mg/kg) as opposed only observed with repeat exposure in adults. Pretreatment with anticholinergics may reduce this risk [13]
Endocrine and Metabolic: Malignant hyperthermia has been reported with an increased risk with concomitant use of volatile anesthetics. Successful outcome depends on recognition of early signs (jaw muscle spasm, acidosis or generalized rigidity to initial administration of succinylcholine for tracheal intubation, or failure of tachycardia to respond to deepening anesthesia). Continuous monitoring of temperature and expired carbon dioxide is recommended and discontinue use of anesthesia and use IV dantrolene sodium as an adjunct to supportive measures [13]
Endocrine and Metabolic: Preexisting electrolyte abnormalities or digitalis toxicity increases the risk for hyperkalemia resulting in serious cardiac arrhythmias or cardiac arrest [13]
Endocrine and Metabolic: Preexisting hypokalemia or hypocalcemia increases risk for prolonged neuromuscular blockade. Correct severe electrolyte disturbances and monitor neuromuscular transmission during therapy [13].
Gastrointestinal: Consider avoiding use in patients with chronic abdominal infection or verify baseline potassium levels are within normal range prior to administration due to the increased risk of developing severe hyperkalemia [13].
Gastrointestinal: Increased intragastric pressure may occur and increases the risk for regurgitation and aspiration of stomach contents. Evaluate patients at risk for aspiration and

regurgitation. Monitor patients during induction of anesthesia and neuromuscular blockage for clinical signs of vomiting and aspiration [13].
Immunologic: Severe, life-threatening and fatal anaphylactic reactions have been reported; cross reactivity may occur in individuals hypersensitive to other neuromuscular blockers (depolarizing and non-depolarizing). Assess patients for previous anaphylactic reactions to neuromuscular blocking agents before treatment initiation [13].
Musculoskeletal: Hyperkalemic rhabdomyolysis has been reported in pediatric and adolescent patients, especially males and mostly 8 years of age or younger. Obtain a history and physical as well as a preoperative creatine kinase. Careful monitoring of ECG can alert the practitioner to peaked T-waves (an early sign). Administration of IV calcium, bicarbonate, and glucose with insulin with hyperventilation have resulted in successful resuscitation in some cases [13].
Musculoskeletal: A transition to non-depolarizing Phase II block may occur with prolonged exposure; indicated by reduced responses to successive stimuli and manifested by respiratory muscle paralysis or weakness. For suspected Phase II block, positive diagnosis should be made by peripheral nerve stimulation prior to administration of anticholinesterase drug [13].
Musculoskeletal: Use with caution in patients with fractures or muscle spasm as induced muscle fasciculations may result in additional trauma. Monitor neuromuscular transmission and the development of fasciculation during therapy [13].
Neurologic: Consider avoiding use in patients with subarachnoid hemorrhage or conditions causing degeneration of central or peripheral nervous systems or verify baseline potassium levels are within normal range prior to administration due to the increased risk of developing severe hyperkalemia [13].
Neurologic: Transient increases in intracranial pressure may occur; adequate anesthesia prior to administration reduces this risk [13].
Ophthalmic: Increased intraocular pressure has been reported; unless benefits of treatment outweigh potential risks, avoid use in patients with narrow angle glaucoma, penetrating eye injury or other conditions adversely effected by increased intraocular pressure [13].
Special populations: Use not recommended in patients with known reduced plasma cholinesterase (pseudocholinesterase) activity [13].
Special populations: Patients with diminished plasma cholinesterase activity including patients with genetic abnormalities of plasma cholinesterase (eg, patients heterozygous or homozygous for atypical plasma cholinesterase gene), pregnant patients, patients with severe liver or kidney disease, malignant tumors, infections, burns, anemia, decompensated heart disease, peptic ulcer, myxedema, patients with chronic oral contraceptive, glucocorticoid, or certain monoamine oxidase inhibitor use, and the use of drugs that irreversibly inhibit plasma cholinesterase (eg, organophosphate insecticides, echothiophate, and certain antineoplastics) are at increased risk neuromuscular blocking effect [13].
Special populations: Patients homozygous for atypical plasma cholinesterase gene are extremely sensitive to the neuromuscular blocking effect; if treatment is initiated, treat resulting apnea or prolonged muscle paralysis with controlled respiration [13].

Adverse Effects

Cardiac arrest, malignant hyperthermia, arrhythmias, bradycardia, tachycardia, hypertension, hypotension, hyperkalemia, prolonged respiratory depression, and apnea have been reported [10].

Black Box Warning

Ventricular Dysrhythmias, Cardiac Arrest, and Death from Hyperkalemic Rhabdomyolysis in Pediatric Patients[13]

- Acute rhabdomyolysis with hyperkalemia followed by ventricular dysrhythmias, cardiac arrest, and death has occurred after the administration of succinylcholine to apparently healthy pediatric patients who were subsequently found to have undiagnosed skeletal muscle myopathy, most frequently Duchenne muscular dystrophy.
- When a healthy appearing pediatric patient develops cardiac arrest within minutes after administration of succinylcholine chloride, not felt to be due to inadequate ventilation, oxygenation or anesthetic overdose, immediate treatment for hyperkalemia should be instituted. In the presence of signs of malignant hyperthermia, appropriate treatment should be instituted concurrently.
- Reserve the use of succinylcholine chloride in pediatric patients for emergency intubation or instances where immediate securing of the airway is necessary, eg, laryngospasm, difficult airway, full stomach, or for intramuscular use when a suitable vein is inaccessible.

Monitoring

Toxic Laboratory Monitoring
Obtain a preoperative creatine kinase [10].

Toxic Physical Monitoring
Monitor oxygen saturation, heart rate, and blood pressure continuously [3].
Closely monitor ECG for peaked T-waves, an early sign of potential cardiac arrest secondary to acute rhabdomyolysis with hyperkalemia [10].
Obtain a history and physical to identify developmental delays suggestive of a myopathy [10].
Assess patients for previous anaphylactic reactions to other neuromuscular blocking agents prior to therapy [10].
Monitor temperature and expired carbon dioxide continuously for early recognition of malignant hyperthermia [10].
Observe for early signs of malignant hyperthermia, including jaw muscle spasm, acidosis, or generalized rigidity to initial administration of succinylcholine for tracheal intubation, or failure of tachycardia to respond to deepening anesthesia [10].
Assess for the presence of a Phase II block, manifesting as prolonged respiratory muscle paralysis or weakness, by using peripheral nerve stimulation [10].
Monitor neuromuscular transmission and the development of fasciculations during therapy [10].
Monitor patients for clinical signs of vomiting and aspiration during induction of anesthesia and neuromuscular blockade [10].
Monitor patients to ensure that the level of anesthesia is adequate [10].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Succinylcholine is an ultra short-acting depolarizing-type, skeletal muscle relaxant. Has no effect on pain threshold, consciousness, or cerebration. Onset of paralysis after IV administration is 30 to 60 seconds with a duration of action of 4 to 6 minutes [15][16]. Onset of action after IM administration is 2 to 4 minutes with a duration of action of 19 to 23 minutes [1][17]. Rapidly hydrolyzed by plasma cholinesterase to succinylmonocholine (which possesses clinically insignificant depolarizing muscle relaxant properties) and then more slowly to succinic acid and choline. Approximately 10% of the drug is eliminated in the urine as unchanged drug [1].

ABOUT

Special Considerations/Preparation

Availability: Available in 100 mg/mL single-use vials and 20 mg/mL multiple-dose vials [10].
Storage: Store under refrigerated conditions between 2 and 8 degrees C (36 and 46 degrees F). Once diluted, discard within 24 hours. The multiple-dose vials are stable at room temperature for 14 days after opening [10].
Preparation: Dilute in D5W or NS to a concentration of 1 or 2 mg/mL [10].

Sucrose

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Preterm infants: 0.5 to 1 mL of 12% to 24% sucrose solution.
Term infants: 2 mL of 12% to 24% sucrose solution.
Administer sucrose solution directly to the tongue 2 minutes prior to the painful procedure.
For patients able to suck, a pacifier should be offered immediately after sucrose administration.
Alternatively, a pacifier dipped in sucrose solution can be offered 2 minutes prior to the procedure.

Uses

Mild analgesia and behavioral comforting prior to painful procedures (eg, vaccination, heel lances) in infants [1][2][3][4][5][6][7]. A combination of sucrose plus non-nutritive sucking was more effective than no intervention and more effective than either single intervention alone in 180 full-term neonates (greater than 2200 g) older than 24 hours undergoing a heel-stick procedure. The dose of sucrose was 2 mL of sucrose 30% administered 2 minutes before the procedure [8].

MEDICATION SAFETY

Adverse Effects

Sucrose 24% has an osmolarity of approximately 1000 mOsm/L. The adverse effects of repeated doses in premature infants are unknown.

Monitoring

Assess for signs of pain and discomfort.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Sucrose administration provides a calming effect and reduces acute procedural pain in both preterm and term infants. The potential mechanism of these effects includes activation of the endogenous opioid system through taste receptors on the tip of the tongue. The time to maximal effect is approximately 2 minutes and the duration of effect is approximately 5 to 10 minutes. The beneficial effects of sucrose can be improved by nonnutritive sucking.

ABOUT

Special Considerations/Preparation

Sweet-Ease®, a 24% sucrose and water solution, is aseptically packaged in an 15 ml cup with a peel off lid that is suitable for dipping a pacifier or for administration via a dropper.

THAM acetate

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

1 to 2 mmol/kg (3.3 to 6.6 mL/kg) per dose IV.
Dose (of the 0.3 M solution) may be calculated from the following formula:

Dose (mL) = Weight (kg) x Base deficit (mEq/L)

Maximum dose in neonates with normal renal function is approximately 5 to 7 mmol/kg per 24 hours. Clinical studies support only short-term use.

Uses

Treatment of metabolic acidosis, primarily in mechanically ventilated patients with significant hypercarbia or hypernatremia. **Do not use in patients who are anuric or uremic.** THAM is not indicated for treatment of metabolic acidosis caused by bicarbonate deficiency.

Administration

Administer by slow IV infusion over at least 30 to 60 minutes. Rate of infusion should not exceed 2 mmol/kg in 30 minutes or 5 mmol/kg in 60 minutes [1]. Infusion into a large vein is recommended (peripheral or umbilical vein may be used) [2][3]. Has also been administered with 25% to 50% of the calculated dose given intravenously over 5 to 10 minutes with the remainder given intravenously over 1 to 6 hours [1][4].

MEDICATION SAFETY

Contraindications/Precautions

Most reports of toxicity in neonates (hypoglycemia, hyperkalemia, liver necrosis) were related to rapid umbilical venous infusion of high doses of THAM base solutions that were more alkaline and hypertonic than the THAM acetate solution currently available from Abbott (pH 8.6; osmolarity 380 mOsm/L). **Irritating to veins**.

Solution Compatibility

No data are currently available on solutions and additives.

Monitoring

Observe IV site closely for signs of extravasation. Follow blood-gas results to assess therapeutic efficacy. Follow urine output. Monitor for respiratory depression, hypoglycemia, and hyperkalemia when using several doses.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

THAM (Tris-Hydroxymethyl Aminomethane) is a proton acceptor that generates NH_3^+ and HCO_3- without generating CO_2. The protonated R-NH_3^+ is eliminated by the kidneys. Unlike bicarbonate, THAM does not require an open system for CO_2 elimination in order to exert its buffering effect.

ABOUT

Special Considerations/Preparation

Supplied as a 0.3-M solution (1 mmol = 3.3 mL) in a 500-mL single-dose container with no bacteriostatic agent. Intended for single-dose use and unused portion should be discarded.

Ticarcillin/Clavulanate

DOSING/ADMINISTRATION

Dose

Timentin injection is no longer marketed in the United States [1].
75 to 100 mg/kg/dose IV infusion by syringe pump over 30 minutes.

Antibiotic Dosing Chart:
Renal function and drug elimination are most strongly correlated with Postmenstrual Age (PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.

Dosing Interval Chart		
PMA (weeks)	**PostNatal (days)**	**Interval (hours)**
≤29	0 to 28 >28	12 8
30 to 36	0 to 14 >14	12 8
37 to 44	0 to 7 >7	12 8
≥45	ALL	6

Uses

Timentin injection is no longer marketed in the United States [1].
Treatment of non-CNS infections, caused by susceptible β-lactamase producing bacteria, including many strains of *E. coli, Enterobacter, Klebsiella, Haemophilus influenzae, Proteus mirabilis, Pseudomonas spp.,* and *Staph. aureus*.

Administration

Dilute in NS, D_5W, or LR to a final concentration of 10 to 100 mg/mL and administer IV over 30 minutes [2].

MEDICATION SAFETY

Contraindications/Precautions

Seizures may occur when administered at very high doses and in the presence of renal impairment. Sodium content should be considered when treating patients requiring salt restrictions (4.5 mEq (103.6 mg) of sodium per gram of ticarcillin/clavulanate).

Adverse Effects

Eosinophilia. Hyperbilirubinemia. Elevations in ALT, AST, BUN, and serum creatinine. Hypernatremia may be exacerbated in ELBW patients.

Solution Compatibility

D_5W, LR, and NS.

Terminal Injection Site Compatibility

Aztreonam, cefepime, famotidine, fluconazole, heparin, insulin, milrinone, morphine, propofol, remifentanil, and theophylline.

Terminal Injection Site Incompatibility

Amikacin, azithromycin, gentamicin, netilmicin, sodium bicarbonate, tobramycin, and vancomycin.

Monitoring

Serum concentrations are not routinely monitored. Assess renal function prior to therapy. Measure serum sodium concentrations and hepatic transaminases periodically. Observe IV site for signs of extravasation.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Timentin® combines the extended-spectrum antibiotic ticarcillin with the β-lactamase inhibitor clavulanic acid in a 30:1 ratio. Ticarcillin is primarily eliminated unchanged by renal mechanisms, whereas clavulanate undergoes significant hepatic metabolism. As a result the mean half-life of ticarcillin in neonates is 4.2 hours compared to a mean half-life of 2 hours for clavulanate. CNS penetration is modest (limited data).

ABOUT

Special Considerations/Preparation

Available as powder for injection in 3.1-g vials. Reconstitute vial by adding 13 mL of sterile water for injection. Dilute further with a compatible solution to a concentration between 10 and 100 mg/mL. Dilutions are stable for 24 hours at room temperature, 3 days refrigerated (D_5W), and 7 days refrigerated (NS and LR). Frozen dilutions stable for 7 days for D_5W and 30 days for NS and LR.
Contains 4.5 mEq (103.6 mg) of sodium per gram of ticarcillin/clavulanate.

Tobramycin

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Antibiotic Dosing Chart:
Renal function and drug elimination are most strongly correlated with Postmenstrual Age (PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.

Dosing Chart			
PMA (weeks)	**Postnatal (days)**	**Dose (mg/kg)**	**Interval (hours)**
≤29*	0 to 7 8 to 28 ≥29	5 4 4	48 36 24
30 to 34	0 to 7 ≥8	4.5 4	36 24
≥35	ALL	4	24
* or significant asphyxia, PDA, or treatment with indomethacin			

The above standard dosing regimen attains trough concentrations 1 mg/L or less and 0.5 mg/L or less in 61% and 24%, respectively, of dose simulations (n=5,000). Likewise, peak concentrations of 5 to 12 mg/L, greater than 12 mg/mL, and less than 5 mg/L were attained in 88%, 1%, and 11%, respectively, of dose simulations [1].

Uses

Treatment of infections caused by aerobic gram-negative bacilli (eg, *Pseudomonas, Klebsiella, E coli*). Usually used in combination with a β-lactam antibiotic.

Infective endocarditis: The following recommendations are based on a consensus of experts [6]. The full pediatric guidelines can be found here: https://doi.org/10.1161/CIR.0000000000000298

Organism Directed Therapy		
Organism	First-Choice	Alternative Choice
Streptococci		
Highly susceptible to penicillin G (MBC 0.1 mcg/mL	Penicillin G or CefTRIAXone	Vancomycin or First-generation cephalosporin

or less); includes most viridans streptococci, groups A, B, C, G nonenterococcal, group D streptococci (S bovis, S equinus)		or CefTRIAXone
Relatively resistant to penicillin (MBC 0.2 mcg/mL or more); less-susceptible viridans streptococci or enterococci	Penicillin G or Ampicillin + Gentamicin (for first 2 weeks, or entire course for enterococci)	Vancomycin + Gentamicin for enterococci Ampicillin + CefTRIAXone (for aminoglycoside (AMG)-resistant enterococci or AMG-intolerant patient) CefTRIAXone + gentamicin (not for enterococcal endocarditis)
Resistant to penicillin	Consult an infectious disease specialist.	---
Staphylococci (S aureus or coagulase-negative staphylococci) †		
Penicillin G susceptible (1 mcg/mL or less) (rare)	Penicillin G	Oxacillin or Nafcillin or First-generation cephalosporin or Vancomycin
Penicillin G resistant (0.1 mcg/mL)	Oxacillin or Nafcillin with or without Gentamicin	Vancomycin (for those highly allergic to beta-lactam antibiotics) or First-generation cephalosporin
Oxacillin (MRSA) resistant (4 mcg/mL)	Vancomycin	Daptomycin for right-sided endocarditis, maybe for left-sided

Vancomycin resistant or intolerant	Daptomycin	Unknown
	†When prosthetic material present add riFAMpin + gentamicin (for first 2 weeks) for all staphylococci	
Gram-negative enteric bacilli	CefTAZidime or Cefepime or Cefotaxime or CefTRIAXone Plus gentamicin (or tobramycin or amikacin, depending on susceptibility)	Broad-spectrum penicillin Plus gentamicin (or tobramycin or amikacin)
HACEK group	CefTRIAXone or Cefotaxime or Ampicillin-sulbactam	Ampicillin (when susceptible) Plus aminoglycoside
KEY: AMG = aminoglycosides; HACEK = Haemophilus species, Aggregatibacter species, Cardiobacterium hominis, Eikenella corrodens, and Kingella species; MBC = minimum bactericidal concentration, MRSA = methicillin-resistant Staphylococcus aureus (includes resistance to oxacillin, nafcillin, and cephalosporins)		
Baltimore, 2015		

Sepsis

Optimal treatment for suspected, early-onset sepsis is broad-spectrum antimicrobial coverage using a combination of ampicillin and an aminoglycoside (usually gentamicin); once a pathogen is identified, therapy should be narrowed unless synergism is required. Therapy should be discontinued at 48 hours if the probability of sepsis is low. Duration of treatment is usually 10 days for bacteremia without an identifiable focus [7].

There was no difference in failure rate between a 7-day vs 10-day duration of empiric treatment with IV cefTRIAXone and amikacin for culture-proven sepsis in 132 neonates, 1.5 kg or more and gestational age 32 weeks or more, who remitted clinically by day 5 in a randomized study. The follow-up period was 28 days. The median age at presentation was 3 days (2 to 4 days) and 56.8% had early-onset sepsis. The majority of organisms in blood cultures were *Klebsiella* spp. (40.9%), *Staphylococcus aureus* (22.7%), *Enterobacter* spp. (16.7%), and MRSA (7.6%) [8].

Administration

Intravenous: Dilute in appropriate volume (as small as 25 mL may be used [2]) of NS or D_5W [3] to concentrations of 2, 4, or 10 mg/mL [4] and infuse over 20 to 60 minutes [3].
Administer as a separate infusion from penicillin-containing compounds.

Intramuscular: For the IM route, solution does not need to be further diluted (10 mg/mL)[5].
IM injection is associated with variable absorption, especially in the very small infant.

MEDICATION SAFETY

Contraindications/Precautions

Precautions
Concomitant use: Avoid concomitant or sequential use of the inhalation formulation with drugs that have neurotoxic, ototoxic, or nephrotoxic potential [10]
Dermatologic: Serious and sometimes fatal allergic reactions, including anaphylaxis and dermatologic reactions (eg, exfoliative dermatitis, toxic epidermal necrolysis, erythema multiforme, and Stevens-Johnson syndrome) have been reported; discontinue use if occurs [9]
Dermatologic: Significant absorption leading to neurotoxicity or nephrotoxicity may occur following local irrigation or application [9]
Immunologic: Cross-sensitivity to other aminoglycoside antibiotics may occur [9]
Immunologic: Topical sensitivity reaction may occur [9]
Immunologic: Overgrowth of nonsusceptible organisms may occur [9]
Immunologic: *Clostridium difficile*-associated diarrhea has been reported; discontinuation may be needed [9]
Immunologic: Contains sodium metabisulfite, a sulfite that may cause allergic-type reactions (eg, anaphylactic symptoms or asthmatic episodes) in susceptible patients [9]
Neuromuscular: Neuromuscular disorders (eg, myasthenia gravis); aminoglycosides may aggravate muscle weakness [10]
Neurologic: Neuromuscular blockade and respiratory paralysis may occur in anesthetized patients who also received neuromuscular blocking drugs (eg, succinylcholine, tubocurarine, or decamethonium), or large transfusions with citrate-anticoagulated blood; calcium salts may reverse blockade [9]
Ophthalmic: Not approved for intraocular or subconjunctival use as macular necrosis has been reported [9]
Otic: Auditory or vestibular dysfunction [10]; particularly with high doses or prolonged therapy, previous courses of ototoxic therapy, and dehydration; monitoring recommended [9]
Renal: Use with caution in patients with renal impairment, due to an increased risk of ototoxicity and nephrotoxicity; monitoring recommended [9]
Renal: Nephrotoxicity may occur and discontinuation may be necessary [10]; monitoring recommended [9]
Reproductive: Pregnancy; may cause fetal harm [10]
Respiratory: Bronchospasm may occur with inhalation tobramycin [10].

Special populations: Reduced serum concentrations may occur in patients with extensive burns; monitoring recommended [9]
Special populations: Reduced serum concentrations may occur in patients with cystic fibrosis; monitoring recommended [9]

Adverse Effects

Transient and reversible renal tubular dysfunction may occur, resulting in increased urinary losses of sodium, calcium, and magnesium. Vestibular and auditory ototoxicity may occur. The addition of other nephrotoxic and/or ototoxic medications (e.g. furosemide, vancomycin) may increase these adverse effects. Increased neuromuscular blockade (i.e. neuromuscular weakness and respiratory failure) may occur when used with pancuronium or other neuromuscular blocking agents and in patients with hypermagnesemia.

Black Box Warning

Warnings
•Patients treated with tobramycin injection and other aminoglycosides should be under close clinical observation, because these drugs have an inherent potential for causing ototoxicity and nephrotoxicity [9].
•Neurotoxicity, manifested as both auditory and vestibular ototoxicity, can occur. The auditory changes are irreversible, are usually bilateral, and may be partial or total. Eighth nerve impairment and nephrotoxicity may develop, primarily in patients having preexisting renal damage and in those with normal renal function to whom aminoglycosides are administered for longer periods or in higher doses than those recommended. Other manifestations of neurotoxicity may include numbness , skin tingling, muscle twitching, and convulsions. The risk of aminoglycoside-induced hearing loss increases with the degree of exposure to either high peak or high trough serum concentrations. Patients who develop cochlear damage may not have symptoms during therapy to warn them of eighth-nerve toxicity, and partial or total irreversible bilateral deafness may continue to develop after the drug has been discontinued [9].
•Rarely, nephrotoxicity may not become apparent until the first few days after cessation of therapy. Aminoglycoside-induced nephrotoxicity usually is reversible [9].
•Renal and eighth-nerve function should be closely monitored in patients with known or suspected renal impairment and also in those whose renal function is initially normal but who develop signs of renal dysfunction during therapy. Peak and trough serum concentrations of aminoglycosides should be monitored periodically during therapy to assure adequate levels and to avoid potentially toxic levels. Prolonged serum concentrations above 12 mcg/mL should be avoided. Rising trough levels (above 2 mcg/mL) may indicate tissue accumulation. Such accumulation, excessive peak concentrations, advanced age, and cumulative dose may contribute to ototoxicity and nephrotoxicity. Urine should be examined for decreased specific gravity and increased excretion of protein, cells, and casts. Blood urea nitrogen, serum creatinine, and creatinine clearance should be measured periodically. When feasible, it is recommended that serial audiograms be obtained in patients old enough to be tested, particularly high-risk patients. Evidence of impairment of renal, vestibular, or auditory

function requires discontinuation of the drug or dosage adjustment [9].
•Tobramycin injection should be used with caution in premature and neonatal infants because of their renal immaturity and the resulting prolongation of serum half-life of the drug [9].
•Concurrent and sequential use of other neurotoxic and/or nephrotoxic antibiotics, particularly other aminoglycosides (e.g., amikacin, streptomycin, neomycin, kanamycin, gentamicin, and paromomycin), cephaloridine, viomycin, polymyxin B, colistin, cisplatin, and vancomycin, should be avoided. Other factors that may increase patient risk are advanced age and dehydration [9].
•Aminoglycosides should not be given concurrently with potent diuretics, such as ethacrynic acid and furosemide. Some diuretics themselves cause ototoxicity, and intravenously administered diuretics enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue [9].
•Aminoglycosides can cause fetal harm when administered to a pregnant woman [9].

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Acyclovir, alprostadil, amiodarone, aztreonam, calcium gluconate, cefoxitin, ceftazidime, clindamycin, dopamine, enalaprilat, esmolol, fluconazole, furosemide, insulin, heparin (concentrations less than or equal to 1 unit/mL), linezolid, magnesium sulfate, metronidazole, midazolam, milrinone, morphine, nafcillin, nicardipine, ranitidine, remifentanil, theophylline, and zidovudine.

Terminal Injection Site Incompatibility

Ampicillin, azithromycin, cefepime, imipenem/cilastatin, indomethacin, heparin (concentrations greater than 1 unit/mL), mezlocillin, oxacillin, penicillin G, propofol, and ticarcillin/clavulanate.

Monitoring

Measure serum concentrations when treating for more than 48 hours. Obtain peak concentration 30 minutes after IV infusion or 1 hour after IM injection, and trough concentration just prior to the next dose [5]. When treating patients with serious infections or significantly changing fluid or renal status consider measuring the serum concentration 24 hours after a dose, and use the chart below for the suggested dosing interval. Blood samples

obtained to monitor serum drug concentrations should be spun and refrigerated or frozen as soon as possible.

Therapeutic serum concentrations:
Peak: 5 to 12 mcg/mL (or C_{max}/MIC ratio greater than 8:1)
Trough: 0.5 to 1 mcg/mL

24- hour Concentration Suggested Dosing Intervals		
Concentration at 24 hours (mg/L)	**Half-life (hours)**	**Suggested Dosing Interval (hours)**
≤1	~ 8	24
1.1 to 2.3	~ 12	36
2.4 to 3.2	~ 15	48
≥3.3	--	Measure level in 24 hours

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action: Tobramycin is an aminoglycoside antibiotic that is bactericidal at low concentrations against most gram-negative bacilli [11].

Dosing recommendations are based on: (1) Higher peak concentrations increase concentration-dependent bacterial killing; (2) There is a post-antibiotic effect on bacterial killing, especially when treating concurrently with a β-lactam antibiotic; (3) There may be less toxicity with less frequent dosing, due to less renal drug accumulation and (4) there may be a decreased risk for adaptive resistance [12][2].
Inactivation of tobramycin by penicillin-containing compounds appears to be a time-, temperature-, and concentration-dependent process. This is probably clinically significant only when penicillin-containing compounds are mixed in IV solutions or when the blood is at room temperature for several hours before the assay is performed.

Vd: Volume of distribution is increased in patients with patent ductus arteriosus (PDA).
Clearance: Clearance is decreased in patients with PDA.
Half-life: Serum half-life is prolonged in premature and asphyxiated newborns.

ABOUT

Special Considerations/Preparation

Pediatric injectable solution available in a concentration of 10 mg/mL. Also available as 40 mg/mL [5]

DOSING/ADMINISTRATION

Dose

Prevention of Hypoxic-ischemic Encephalopathy (HIE), Adjunct to Hypothermia
Combined frequency of mortality and severe neurological disability was not reduced in a pilot study (n=44) [1].

Uses

Adjunct for neuroprotection against hypoxic-ischemic encephalopathy (HIE): Combined frequency of mortality and severe neurological disability at 18 to 24 months of age was not reduced when topiramate was added to whole-body hypothermia in a randomized pilot study of 44 asphyxiated term-newborns with HIE. The dosage of topiramate was 10 mg/kg/day orally via orogastric tube once daily for the first 3 days of life. No adverse effects were related to topiramate [1].
Topiramate has been safely used, in concert with deep or mild hypothermia, for HIE in full-term newborns (n=27). An initial dose of 5 mg/kg (by orogastric tube) was started at initiation of hypothermia, followed by doses of either 5 mg/kg or 3 mg/kg given on days 2 and 3 [2]. .

Seizure disorders: The addition of topiramate controlled or reduced acute seizure activity in 4 of 6 term infants having a variety of seizure syndromes refractory to phenobarbital or phenobarbital + phenytoin in a retrospective review of use in term newborns (n=6). At follow-up (5 to 11.5 months), 5 of 6 patients were seizure-free on topiramate monotherapy. Of these 5 patients, 4 received topiramate 10 mg/kg/day; the remaining patient received 3 mg/kg/day [7].

Pediatric FDA Approved Indications
Immediate-release: Indicated for partial-onset or primary generalized tonic-clonic seizures in patients 2 years or older (initial monotherapy) and ages 2 years or older (adjunctive therapy). Indicated for seizures associated with Lennox-Gastaut syndrome in patients 2 years or older. Indicated for the prophylaxis of migraine headache in adolescents 12 years or older. The efficacy of topiramate in the acute treatment of migraine has not been studied [8][9][10].

Extended-release: Indicated as initial monotherapy for partial-onset or primary generalized tonic-clonic seizures in patients 2 years or older (Qudexy® XR) and 6 years or older (Trokendi XR™) [5][6]. Indicated as an adjunct for seizures associated with Lennox-Gastaut syndrome, partial-onset, or primary generalized tonic-clonic seizures in patients 6 years or older (Trokendi XR™) [5] and 2 years or older (Qudexy® XR) [6]. Also indicated for the prophylaxis of migraine headache in adolescent patients 12 years or older [5][6]

Administration

Sprinkle Capsules: May be opened and the sprinkles mixed with water to be administered via orogastric tube [2][3]. Use mixture immediately. Do not store opened capsules for future use [3].

The National Institute for Occupational Safety and Health (NIOSH) recommends the use of single gloves by anyone handling intact tablets or capsules or administering from a unit-dose package [4].
In the preparation of tablets or capsules, including cutting, crushing, or manipulating, or the handling of uncoated tablets, NIOSH recommends the use of double gloves and a protective gown. Prepare in a ventilated control device, if possible. Use respiratory protection if not prepared in a control device. During administration, wear single gloves, and wear eye/face protection if the formulation is hard to swallow or if the patient may resist, vomit, or spit up [4].

MEDICATION SAFETY

Contraindications/Precautions

Acute myopia, associated with secondary angle-closure glaucoma, has been reported with topiramate, generally within the first month of use. Hyperthermia and decreased sweating have been reported, especially in pediatric patients. Metabolic acidosis has been reported, with an increased risk in patients with conditions or therapies that predispose to acidosis (eg, renal disease, severe respiratory disorders, status epilepticus, diarrhea, ketogenic diet, or certain drugs). In patients with or without a history of seizures, topiramate should be gradually withdrawn to minimize the potential for seizures or increased seizure frequency. Hyperammonemia with or without encephalopathy may occur with topiramate with or without concomitant valproic acid [3].

Adverse Effects

When used for neuroprotection in concert with hypothermia for hypoxic-ischemic encephalopathy (n=27), mild and reversible acidosis was seen in patients receiving deep hypothermia (DH); metabolic acidosis was not seen with mild hypothermia (MH). In addition, short-course topiramate did not cause acid-base imbalance, nephrolithiasis, or ophthalmological concerns [2].
When used for seizure disorders, 3 of 6 term infants had a weight of less than the fifth percentile, however, these patients also had poor oromotor control [7].

Monitoring

Monitor for hyperthermia and decreased sweating, especially in hot weather. Measure serum bicarbonate levels at baseline and periodically during treatment. Seizures or increased seizure frequency should be monitored in patients with or without a history of epilepsy if rapid withdrawal of topiramate therapy is required. Examination of ammonia levels is recommended in any patient experiencing unexplained lethargy, vomiting, or changes in mental status, which may be indicative of hyperammonemia with or without encephalopathy [3].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action: The exact mechanism of action of topiramate is unknown; however, 4 properties that may contribute to antiepileptic and antimigraine efficacy include a blockage of voltage-dependent sodium channels, an augmentation of gamma-aminobutyrate acid (GABA) activity at some subtypes of the GABA-A receptors, antagonism of AMPA/kainate subtype of the glutamate receptor, and inhibition of the carbonic anhydrase enzyme, particularly isozymes II and IV [3]. Neuroprotective effects appear to be related to AMPA and kainate receptor inhibition, blockade of sodium channels, high-voltage activated calcium currents, carbonic anhydrase isoenzymes, and mitochondrial permeability transition pore (MPTP) [11].

The average topiramate concentrations were 6.5 to 7 mg/L after the first dose and 12 to 13 mg/L after the third dose in 44 term newborns administered topiramate 10 mg/kg/day orally with hypothermia. Topiramate concentrations were significantly lower in infants coadministered phenobarbital [1].

Topiramate serum concentrations and pharmacokinetics varied, based upon the level of hypothermia and use of concomitant phenobarbital in 13 full-term newborns with hypoxic-ischemic encephalopathy who received either deep hypothermia (DH; n=5) or mild hypothermia (MH; n=8) and either topiramate monotherapy (n=6) or with concomitant phenobarbital (n=7). All patients received a topiramate dose of 5 mg/kg every 24 hours for 3 days, starting with the initiation of hypothermia. Serum concentrations were lower in patients who received both MH and phenobarbital (NS). The coefficient of variability was greater in the DH group than the MH group (p=0.005), likely due to more irregular absorption and elimination. In those patients who attained virtual steady state (n=9), lower AUC, lower average serum concentration, and a longer half-life were seen in the DH compared with the MH group (318.1 +/- 101.6 vs 366.2 +/- 48.1 mg/L/hr, 13.25 +/- 4.2 vs 15.26 +/- 2 mg/L, and 48.82 +/- 4.6 vs 29.03 +/- 23.8 hours, respectively; all NS). Patients who received concomitant phenobarbital had lower minimum serum concentrations than those on topiramate monotherapy (8.7 +/- 2.9 vs 11.67 +/- 0.9 mg/L; p=0.032), with lower maximum and average serum concentrations, lower AUC, shorter half-life, and higher clearance (15.38 +/- 5.3 vs 19.87 +/- 1.9 mg/L, 12.6 +/- 3.7 vs 15.66 +/- 1.6 mg/L, 302.4 +/- 89.7 vs 375.8

+/- 37.4 mg/L/hr, 26.46 +/- 17.7 vs 42.88 +/- 19.1 hours, 17.92 +/- 6.2 vs 13.42 +/- 1.4 mL/kg/hr, respectively; all NS). Serum concentrations within the reference range of 5 to 20 mg/L were achieved in most patients [12].

ABOUT

Special Considerations/Preparation

Oral Sprinkle Capsules: Available as 15-mg and 25-mg sprinkle capsules. Store at or below 25 degrees C (77 degrees F); protect from moisture [3].

Extemporaneous Preparation

Topiramate 6 mg/mL oral suspension is stable for 90 days when refrigerated (preferred) or stored at room temperature. To prepare 100 mL of topiramate 6 mg/mL [13]:

- Crush six 100-mg topiramate **immediate-release** tablets and triturate to a fine powder in a mortar.
- Levigate powder to a uniform paste with a 1:1 concentration of Ora-Plus®:Ora-Sweet® vehicle.
- Geometrically incorporate vehicle with constant mixing; transfer mixture to a graduated cylinder.
- Rinse mortar with vehicle, transfer to cylinder, and add sufficient vehicle to 100 mL.
- Transfer suspension to a plastic prescription bottle; label "Shake Well Before Use" and "Refrigerate".

The National Institute for Occupational Safety and Health (NIOSH) recommends the use of double gloves and a protective gown by anyone compounding a hazardous oral liquid or any hazardous drug for feeding tube. If possible, prepare in a control device. Respiratory, eye, and face protection are needed if not done in a control device [4].

Tropicamide (Ophthalmic)

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

1 drop instilled in the eye at least 10 minutes prior to funduscopic procedures.
Use **only** the 0.5% ophthalmic solution in neonates.
Apply pressure to the lacrimal sac during and for 2 minutes after instillation to minimize systemic absorption.

Uses

Induction of mydriasis and cycloplegia for diagnostic and therapeutic ophthalmic procedures.

MEDICATION SAFETY

Adverse Effects

Feedings should be withheld for 4 hours following procedure. Systemic effects are those of anticholinergic drugs: Fever, tachycardia, vasodilatation, dry mouth, restlessness, decreased gastrointestinal motility, and urinary retention. The use of solutions with concentrations of 1% or greater have caused systemic toxicity in infants.

Monitoring

Monitor heart rate and assess for signs of ileus prior to feeding.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Anticholinergic drug that produces pupillary dilation by inhibiting the sphincter pupillae muscle, and paralysis of accommodation. Mydriasis begins within 5 minutes of instillation; cycloplegia occurs in 20 to 40 minutes. Recovery of accommodation occurs in 6 hours.

Without lacrimal sac occlusion, approximately 80% of each drop may pass through the nasolacrimal system and be available for rapid systemic absorption by the nasal mucosa.

ABOUT

Special Considerations/Preparation

Supplied as ophthalmic solution in 0.5%, and 1% concentrations in 2-, 3-, and 15-mL dropper bottles. Store away from heat. **Do not refrigerate.**
A combination eye drop solution ("Caputo drops") may be prepared in a 15-mL bottle with 3.75 mL of cyclopentolate 2%, 7.5 mL of tropicamide 1%, and 3.75 mL of phenylephrine 10%. The final solution contains cyclopentolate 0.5%, tropicamide 0.5%, and phenylephrine 2.5%.
Use within 24 hours, as the solution contains no preservatives.

Ursodiol

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

10 to 15 mg/kg/dose orally every 12 hours.

Uses

Treatment of cholestasis associated with parenteral nutrition, biliary atresia, and cystic fibrosis. Also used to dissolve cholesterol gallstones.
Cholestasis: During first course therapy, ursodiol reduced direct bilirubin by 1.89 mg/dL compared with an increase of 0.76 mg/dL (p = 0.03) for phenobarbital in a retrospective study of 68 preterm and term newborns with direct bilirubin greater than 3 mg/dL. The change for all treatment courses were -3.96 mg/dL for ursodiol and +0.28 mg/dL for phenobarbital. Median dosages were ursodiol 27.43 mg/kg/day enterally and phenobarbital 4.48 mg/kg/day IV [1].

MEDICATION SAFETY

Contraindications/Precautions

Contraindications
• Complete biliary obstruction [2]
Patients with calcified cholesterol, radiopaque, or radiolucent bile pigment stones [3]
• Patients with compelling reasons for cholecystectomy, including unremitting acute cholecystitis, cholangitis , biliary obstruction, gallstone pancreatitis, or biliary-gastrointestinal fistula [3]
• Allergy to bile acids [3]

Adverse Effects

Nausea/vomiting, abdominal pain, constipation, and flatulence.

Monitoring

Hepatic transaminases and direct bilirubin concentration.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Ursodiol is a hydrophilic bile acid that decreases both the secretion of cholesterol from the liver and its intestinal absorption. It is well absorbed orally. After conjugation with taurine or glycine, it then enters the enterohepatic circulation where it is excreted into the bile and intestine. It is hydrolyzed back to the unconjugated form or converted to lithocholic acid which is excreted in the feces. Serum half-life is 3 to 4 days in adults. Dissolution of gallstones may take several months. Aluminum-containing antacids bind ursodiol and inhibit absorption.

ABOUT

Special Considerations/Preparation

Availability: 250-mg and 500-mg tablet and 300-mg capsules.

Extemporaneous Compounds
20 mg/mL
To prepare 255 mL of ursodiol 20 mg/mL: Empty seventeen (17) 300 mg ursodiol capsules into a mortar and triturate into a fine powder. Using a small amount of vehicle (choice of 1:1 Ora-Sweet/Ora-Plus OR 1:1 methylcellulose 1%/cherry syrup NF), add to powder and mix into a paste. Continue to add vehicle in geometric portions until close to volume, mixing well after each addition. Transfer the suspension to a graduate and add vehicle quantity sufficient to 255 mL. Transfer suspension to prescription bottle; label with "Shake Well Before Use" and "Refrigerate." Ursodiol 20 mg/mL suspension is stable for 91 days when refrigerated (preferred) or stored at room temperature.[4].
25 mg/mL
A 25-mg/mL oral liquid suspension may be made by opening ten (10) 300-mg capsules into a glass mortar. Mix this powder with 10 mL of glycerin and stir until smooth. Add 60 mL of Ora-Plus® to the mixture and stir. Transfer the contents of the mortar to a glass amber bottle and shake well. Add a small amount of orange syrup to the mortar and rinse. Pour the remaining contents into the amber glass bottle. Then add enough simple syrup to make the final volume 120 mL, for a final concentration of 25 mg/mL. Shake vigorously. Mixture is **stable for 60 days stored at room temperature or refrigerated**[5].
50 mg/mL
A 50 mg/mL oral liquid suspension was made by triturating twelve (12) 250 mg tablets into a

glass mortar. 30 mL of Ora-Plus and 30 mL of either strawberry syrup or Ora-Sweet SF was mixed to a final volume of 60 mL. Strawberry syrup was prepared by mixing 3200 mL of simple syrup, NF, and 600 mL of strawberry fountain syrup. Mixture is **stable for 90 days refrigerated (3° to 5°C) or room temperature (23° to 25°C)** in amber plastic bottles [6]

60 mg/mL

A 60-mg/mL oral liquid suspension may be made by opening twelve (12) 300-mg capsules into a glass mortar. Mix with sufficient amount of glycerin to make fine paste, then add simple syrup for a total final volume of 60 mL. Mixture is **stable for 35 days refrigerated**[7].

ValGANciclovir

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Symptomatic Congenital CMV Infection: 16 mg/kg per dose orally every 12 hours. Treat for a minimum of 6 weeks; longer-term treatment may be appropriate [1][2]. Studies have reported continuing prophylaxis for 3 or 6 months [3][4]
Note: Dosing applies only to pharmaceutical grade valGANciclovir. Data are not available for extemporaneous formulations.

Dose Adjustment for Hematologic Toxicity: If absolute neutrophil count (ANC) less than 500 cells/mm^3 (confirm by repeat count), hold drug until ANC greater than 750 cells/mm^3. If the ANC falls again to less than 750 cells/mm^3, reduce the dosage by 50%. If ANC again falls to less than 500 cells/mm^3, discontinue the drug [1].

Uses

Symptomatic congenital CMV infections[8][1][2]. There was no difference between a duration of 6 weeks or 6 months of valGANciclovir in hearing in the better ear from baseline to the 6-month follow-up in neonates (32 weeks or more gestational age weighing at least 1800 g) with symptomatic congenital CMV disease. However, secondary outcomes (hearing at 12 months and 24 months and neurodevelopmental scores) were modestly better with 6 months versus 6 weeks of therapy. There was no difference in grade 3 or 4 neutropenia between the two treatment durations [3].

Cytomegalovirus (CMV)- HIV infection: ValGANciclovir is recommended as a first-line agent for congenital CMV infection in patients with HIV co-infection [9]

Administration

Administer with food.Do not break or crush tablets[5].

•Handle and dispose of according to guidelines for antineoplastic drugs; drug is potentially carcinogenic and mutagenic [6]
•Avoid direct contact of broken or crushed tablets, the powder for oral solution, and the reconstituted oral solution with the skin or mucous membranes [6].
•The National Institute for Occupational Safety and Health (NIOSH) recommends the use of single gloves by anyone handling intact tablets or capsules or administering from a unit-dose package [7].

•NIOSH recommends the use of double gloves and a protective gown by anyone handling a hazardous oral liquid or any hazardous drug via a feeding tube. Prepare in a control device, if possible. Use respiratory, eye, and face protection if not done in a control device. During administration, eye/face protection is needed if the patient may resist, or if there is potential to vomit or spit up [7].

MEDICATION SAFETY

Contraindications/Precautions

Precautions
Hematologic: Absolute neutrophil count less than 500 cells/mcL, hemoglobin less than 8 g/dL, or platelet count less than 25,000/mcL; do not use [10].
Hematologic: Increased risk for hematologic toxicity in patients receiving myelosuppressive drugs or irradiation; with a preexisting cytopenia, previous leukopenia with ganciclovir or other nucleoside analogues, renal impairment, or baseline neutrophil count less than 1,000 cells/mcL; or infants. Monitoring recommended. Consider hematopoietic growth factor treatment in patients with severe leukopenia, neutropenia, anemia, or thrombocytopenia [10]
Renal: Acute renal failure may occur in patients receiving concomitant nephrotoxic drugs or in patients with dehydration [10]
Renal: Renal impairment; dosage reduction recommended [10]

Black Box Warning

Hematologic Toxicity, Impairment of Fertility, Fetal Toxicity, Mutagenesis and Carcinogenesis [10]

- Hematologic Toxicity: Severe leukopenia, neutropenia, anemia, thrombocytopenia, pancytopenia, and bone marrow failure including aplastic anemia have been reported in patients treated with valGANciclovir hydrochloride.
- Impairment of Fertility: Based on animal data and limited human data, valGANciclovir hydrochloride may cause temporary or permanent inhibition of spermatogenesis in males and suppression of fertility in females.
- Fetal Toxicity: Based on animal data, valGANciclovir hydrochloride has the potential to cause birth defects in humans.
- Mutagenesis and Carcinogenesis: Based on animal data, valGANciclovir hydrochloride has the potential to cause cancers in humans.

Monitoring

CBC, including differential, and platelet counts should be monitor frequently, especially in

patients with a history of leukopenia resulting from ganciclovir or other nucleoside analogue use, in infants, in patients with renal impairment, and in those with neutrophil counts less than 1000 cells/mcL at the beginning of treatment. Increase monitoring for cytopenias if therapy with oral ganciclovir is changed to valGANciclovir due to increased plasma concentrations of ganciclovir after valGANciclovir administration. Monitor renal function during therapy. Adjust the dose as appropriate for changes in height and body weight [10].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

valGANciclovir is a prodrug of ganciclovir that is rapidly converted to ganciclovir after oral administration by liver and intestinal esterases. Bioavailability is 40% to 60%, and may be improved by administering with food. Excreted entirely by the kidneys as unchanged drug. Elimination half-life in infants is 3 hours. Dosing adjustments may be required for infants with renal impairment.

ABOUT

Special Considerations/Preparation

Availability: Valcyte® is supplied as a white to slightly yellow powder for constitution, forming a colorless to brownish yellow tutti-frutti flavored solution, which when constituted with water as directed contains **50 mg/mL valGANciclovir** free base. Available in glass bottles containing approximately 100 mL of solution after constitution. The inactive ingredients of Valcyte for oral solution are sodium benzoate, fumaric acid, povidone K-30, sodium saccharin, mannitol and tutti-frutti flavoring.

Reconstitution: Valcyte® for oral solution must be constituted by the pharmacist prior to dispensing to the patient. To prepare the oral solution measure 91 mL of purified water in a graduated cylinder. Shake the Valcyte® bottle to loosen the powder. Remove the cap and add approximately half the total amount of water for constitution to the bottle and shake the closed bottle well for about 1 minute. Add the remainder of water and shake the closed bottle well for about 1 minute. This prepared solution contains 50 mg of valGANciclovir free base per 1 mL.

Storage: Store constituted oral solution under refrigeration at 2 to 8 degrees C (36 to 46 degrees F) for no longer than 49 days. **Do not freeze**.

Extemporaneous Compound

ValGANciclovir 30 mg/mL and 60 mg/mL suspension is stable for 35 days when refrigerated (4 degrees C). To prepare 120 mL of [11]:

- **30 mg/mL**
- Place eight valGANciclovir 450 mg tablets into a mortar. Triturate into a fine powder.

- In 1 mL increments, add Ora-Plus to the powder, mixing to form a paste.
- Through the process of geometric dilution, add a total of 60 mL of Ora-Plus, mixing well after each addition.
- Add the mixture to an amber glass bottle; scrape mortar and pestle for leftover residue and add to bottle.
- Rinse mortar and pestle with 10 mL of Ora-Sweet and add to bottle; repeat the rinsing process four times.
- Add enough Ora-Sweet to the bottle to bring the total volume to 120 mL; shake well.
- Label the bottle with "Shake Well Before Use" and "Refrigerate."
- **60 mg/mL**
- Place sixteen valGANciclovir 450 mg tablets into a mortar. Triturate into a fine powder.
- In 1 mL increments, add Ora-Plus to the powder, mixing to form a paste.
- Through the process of geometric dilution, add a total of 60 mL of Ora-Plus, mixing well after each addition.
- Add the mixture to an amber glass bottle; scrape mortar and pestle for leftover residue and add to bottle.
- Rinse mortar and pestle with 10 mL of Ora-Sweet and add to bottle; repeat the rinsing process four times.
- Add enough Ora-Sweet to the bottle to bring the total volume to 120 mL; shake well.
- Label the bottle with "Shake Well Before Use" and "Refrigerate."

90 mg/mL suspension was stable for at least 125 days when refrigerated (2°to 8°C). To prepare 225 mL [12]:

- Triturate forty-five valGANciclovir 450 mg tablets into a fine powder in a glass mortar.
- Slowly add 45 mL of the sodium benzoate solution * and work the powder into a smooth paste using a pestle. All film coating should dissolve
- Add 50 mL of the cherry-chocolate vehicle **, mix well, and transfer to a beaker that has been calibrated to 225 mL with a graduated cylinder.
- Rinse mortar and pestle with two 50 mL portions of the cherry-chocolate vehicle and transfer the liquid from each rinse into the beaker.
- 10*N* hydrochloric acid should be added to adjust pH to approximately 3.2. This may require the addition of 0.4 to 0.45 mL of the 10*N* hydrochloric acid.
- Add cherry-chocolate vehicle to bring the final volume to 225 mL.
- Add more 10*N* hydrochloric acid, if necessary, to adjust the pH to approximately 3.2
- Mix well and transfer the preparation to an amber bottle.
- Label "Refrigerate," "Shake Well," and "Cytotoxic Drug Precautions."

* In a glass beaker, dissolve 117 mg of sodium benzoate in 45 mL of Sterile Water for Irrigation, USP and set aside. Sodium benzoate concentration of the final suspension was 0.1%.
** Using a 500 mL graduated cylinder, add 0.6 mL of artificial cherry flavoring to 300 mL of simple syrup and dilute to 500 mL with Hershey's chocolate syrup. Preserve with 0.06%

sodium benzoate. Mix well and set aside. Label with expiration date of one year and store in refrigerator.

The National Institute for Occupational Safety and Health (NIOSH) recommends the use of double gloves and a protective gown by anyone compounding a hazardous oral liquid or preparing any hazardous drug for administration by feeding tube. If possible, prepare in a control device. Respiratory, eye, and face protection are needed if not done in a control device [7]

DOSING/ADMINISTRATION

Dose

Initial dose: 10 to 15 mg/kg/dose IV every 6 to 18 hours.

Initial Dose Intervals		
PMA†	**Postnatal Age†**	**Interval**
29 weeks or less	0 to 14 days older than 14 days	18 hours 12 hours
30 to 36 weeks	0 to 14 days older than 14 days	12 hours 8 hours
37 to 44 weeks	0 to 7 days older than 7 days	12 hours 8 hours
45 weeks or more	ALL	6 hours
† Postmenstrual age (PMA) is gestational age plus postnatal age. PMA is the primary determinant of dosing interval with postnatal age as the secondary qualifier.		
Renal function and drug elimination are strongly correlated with postmenstrual age.		

Serious MRSA infections: 10 to 20 mg/kg IV every 8 to 48 hours depending on postmenstrual age, weight, and serum creatinine; adjust dose to achieve desired AUC/MIC ratio. **MAX dose, 3600 mg/day;** most children do not require doses higher than 3000 mg/day [1].

Anthrax (as part of combination therapy) [2][3].
32 weeks or more gestational age
Serum creatinine (SCr) less than 0.7 mg/dL: 20 mg/kg IV loading dose; then 15 mg/kg/dose every 12 hours
SCr 0.7 to 0.9 mg/dL: 20 mg/kg IV loading dose; then 20 mg/kg/dose every 24 hours
SCr 1 to 1.2 mg/dL: 20 mg/kg IV loading dose; then 15 mg/kg/dose every 24 hours
SCr 1.3 to 1.6 mg/dL: 20 mg/kg IV loading dose; then 10 mg/kg/dose every 24 hours
SCr greater than 1.6 mg/dL: 20 mg/kg IV loading dose; then 15 mg/kg/dose every 48 hours
Duration: 2 to 3 weeks or more until stable. Continue antimicrobial course of prophylaxis (usually oral therapy) for up to 60 days from onset of illness

Dose Adjustments
Extracorporeal membrane oxygenation: A starting dose of 25 mg/kg/dose IV every 18 hours was predicted to achieve an area under the curve $_{0 \text{ to } 24 \text{ hours}}$ greater than 400 mg x hr/L in neonates undergoing extracorporeal membrane oxygenation in a retrospective

population pharmacokinetic simulation (n=93). Trough concentration goal was less than 15 mg/L [4]

Uses

Drug of choice for serious infections caused by methicillin-resistant staphylococci (eg, *S aureus* and *S epidermidis*) and penicillin-resistant pneumococci.

Anthrax[2]:

Systemic Anthrax when meningitis can be ruled out (IV)
Combination IV Therapy

- **Preferred:** Ciprofloxacin. *Alternatives in order of preference: meropenem, levofloxacin, imipenem/cilastatin, or vancomycin. If strains are penicillin- susceptible, then penicillin G (preferred) or ampicillin (alternative).*
- **Plus**
- **Preferred:** Clindamycin *Alternatives in order of preference: linezolid, doxycycline (not for neonates 37 weeks gestation or younger), or rifampin.*

*Clostridium difficile***infection:** Young children and infants may be asymptomatically colonized, but are unlikely to be infected with *C difficile*. Routine testing for *C difficile* in neonates or infants 12 months or younger with diarrhea is not recommended [9] .

Clinical Definition	Recommendation
Initial episode, non-severe	MetroNIDAZOLE or Vancomycin
Initial episode, severe/fulminant	Vancomycin +/- IV metroNIDAZOLE (when critical illness is present)
First recurrence, non-severe	MetroNIDAZOLE or Vancomycin
Second or subsequent recurrence	Vancomycin •For 10 days followed by rifAXIMin* for 20 days OR •As a tapered and pulsed regimen OR Fecal microbiota transplantation (after multiple recurrences)
McDonald, 2017	
* Pediatric dosing not available for rifAXIMin; no FDA approved uses for patients younger than 12 years.	

Infective endocarditis: The following recommendations are based on a consensus of experts [10]. The full pediatric guidelines can be found here: https://doi.org/10.1161/CIR.0000000000000298

Organism Directed Therapy		
Organism	First-Choice	Alternative Choice
Streptococci		
Highly susceptible to penicillin G (MBC 0.1 mcg/mL or less); includes most viridans streptococci, groups A, B, C, G nonenterococcal, group D streptococci (S bovis, S equinus)	Penicillin G or CefTRIAXone	Vancomycin or First-generation cephalosporin or CefTRIAXone
Relatively resistant to penicillin (MBC 0.2 mcg/mL or more); less-susceptible viridans streptococci or enterococci	Penicillin G or Ampicillin + Gentamicin (for first 2 weeks, or entire course for enterococci)	Vancomycin + Gentamicin for enterococci Ampicillin + CefTRIAXone (for aminoglycoside (AMG)-resistant enterococci or AMG-intolerant patient) CefTRIAXone + gentamicin (not for enterococcal endocarditis)
Resistant to penicillin	Consult an infectious disease specialist.	---
Staphylococci (S aureus or coagulase-negative staphylococci) †		
Penicillin G susceptible (1 mcg/mL or less) (rare)	Penicillin G	Oxacillin or Nafcillin or First-generation cephalosporin or Vancomycin

Penicillin G resistant (0.1 mcg/mL)	Oxacillin or Nafcillin with or without Gentamicin	Vancomycin (for those highly allergic to beta-lactam antibiotics) or First-generation cephalosporin
Oxacillin (MRSA) resistant (4 mcg/mL)	Vancomycin	Daptomycin for right-sided endocarditis, maybe for left-sided
Vancomycin resistant or intolerant	Daptomycin	Unknown
	†When prosthetic material present add riFAMpin + gentamicin (for first 2 weeks) for all staphylococci	
Gram-negative enteric bacilli	CefTAZidime or Cefepime or Cefotaxime or CefTRIAXone Plus gentamicin (or tobramycin or amikacin, depending on susceptibility)	Broad-spectrum penicillin Plus gentamicin (or tobramycin or amikacin)
HACEK group	CefTRIAXone or Cefotaxime or Ampicillin-sulbactam	Ampicillin (when susceptible) Plus aminoglycoside
KEY: AMG = aminoglycosides; HACEK = Haemophilus species, Aggregatibacter species, Cardiobacterium hominis, Eikenella corrodens, and Kingella species; MBC = minimum bactericidal concentration, MRSA = methicillin-resistant Staphylococcus aureus (includes resistance to oxacillin, nafcillin, and cephalosporins)		
Baltimore, 2015		

Organism Directed Therapy		
Organism	First-Choice	Alternative Choice
Streptococci		

Highly susceptible to penicillin G (MBC 0.1 mcg/mL or less); includes most viridans streptococci, groups A, B, C, G nonenterococcal, group D streptococci (S bovis, S equinus)	Penicillin G or CefTRIAXone	Vancomycin or First-generation cephalosporin or CefTRIAXone
Relatively resistant to penicillin (MBC 0.2 mcg/mL or more); less-susceptible viridans streptococci or enterococci	Penicillin G or Ampicillin + Gentamicin (for first 2 weeks, or entire course for enterococci)	Vancomycin + Gentamicin for enterococci Ampicillin + CefTRIAXone (for aminoglycoside (AMG)-resistant enterococci or AMG-intolerant patient) CefTRIAXone + gentamicin (not for enterococcal endocarditis)
Resistant to penicillin	Consult an infectious disease specialist.	---
Staphylococci (S aureus or coagulase-negative staphylococci) †		
Penicillin G susceptible (1 mcg/mL or less) (rare)	Penicillin G	Oxacillin or Nafcillin or First-generation cephalosporin or Vancomycin
Penicillin G resistant (0.1 mcg/mL)	Oxacillin or Nafcillin with or without Gentamicin	Vancomycin (for those highly allergic to beta-lactam antibiotics) or First-generation cephalosporin
Oxacillin (MRSA) resistant (4 mcg/mL)	Vancomycin	Daptomycin for right-sided endocarditis, maybe for left-

		sided
Vancomycin resistant or intolerant	Daptomycin	Unknown
	†When prosthetic material present add riFAMpin + gentamicin (for first 2 weeks) for all staphylococci	
Gram-negative enteric bacilli	CefTAZidime or Cefepime or Cefotaxime or CefTRIAXone Plus gentamicin (or tobramycin or amikacin, depending on susceptibility)	Broad-spectrum penicillin Plus gentamicin (or tobramycin or amikacin)
HACEK group	CefTRIAXone or Cefotaxime or Ampicillin-sulbactam	Ampicillin (when susceptible) Plus aminoglycoside
KEY: AMG = aminoglycosides; HACEK = Haemophilus species, Aggregatibacter species, Cardiobacterium hominis, Eikenella corrodens, and Kingella species; MBC = minimum bactericidal concentration, MRSA = methicillin-resistant Staphylococcus aureus (includes resistance to oxacillin, nafcillin, and cephalosporins)		
Baltimore, 2015		

Sepsis, Prophylaxis; Catheter Removal: Clinical sepsis rates of 2% were observed when infants were receiving antibiotics within 12 hours of removing a peripherally inserted central catheter (PICC) compared with 13% (p=0.03) of infants not on antibiotics within 12 hours of removal in retrospective chart review (n=196 premature infants). Elective vancomycin 15 mg/kg IV was administered 2 hours prior to catheter removal in 27 out of 48 removals. The duration of PICC lines was 24.3 days (range, 8 to 67 days). Susceptibility pattern for vancomycin did not change during the study period [11]. Reductions (11% vs 0%; p=0.021) in culture-confirmed sepsis were demonstrated in a prospective randomized controlled study in 88 preterm infants administered cefazolin 1 hour prior to and 12 hours after removal of a PICC line compared with no antibiotic use [12]. However, this study was criticized for methodology shortcomings that limit its applicability [13]. Sepsis rates were 10.3% with removal of a PICC without antibiotics 48 hours prior to removal compared with 1.5% (p=0.002) in neonates on cefazolin/gentamicin at the time of removal of the PICC in a retrospective study (n=345) [14].

Sepsis
There was no difference in failure rate between a 7-day vs 10-day duration of empiric treatment with IV cefTRIAXone and amikacin for culture-proven sepsis in 132 neonates, 1.5 kg or more and gestational age 32 weeks or more, who remitted clinically by day 5 in a randomized study. The follow-up period was 28 days. The median age at presentation was 3 days (2 to 4 days) and 56.8% had early-onset sepsis. The majority of organisms in blood cultures were *Klebsiella* spp. (40.9%), *Staphylococcus aureus* (22.7%), *Enterobacter* spp. (16.7%), and MRSA (7.6%) [15].

Ventriculitis, Device Associated: All 7 preterm infants (less than 28 weeks gestation) experienced resolution of ventriculitis with intraventricular vancomycin (5 out of 8 events were treated with additional IV vancomycin) in a case series. Ventriculitis resolved in a median of 5.5 days (range, 2 to 31 days). A total of 40 intraventricular vancomycin doses (3, 5, 10, or 15 mg) were administered in 8 ventriculitis events. Intraventricular vancomycin was administered over 2 minutes as a sterile 10-mg/mL solution at the end of the normal reservoir tap followed by a 1-mL sterile NS flush of the ventriculostomy reservoir and catheter. Doses were repeated for CSF concentrations less than 10 mg/L. The longest intervals to maintain CSF vancomycin concentration above 10 mg/L were 45 hours for 3 mg (12.8 mg/L), 97 hours for 5 mg (21.4 mg/L), and 114 hours for 10 mg (19.5 mg/L). Only 2 CSF concentrations were available for the 15-mg dose; 230.7 mg/L at 24 hours post-dose and 44.9 mg/L at 68 hours post-dose. Concomitant IV vancomycin was used in 5 of the 8 events; median vancomycin trough was 6.1 mg/L (range, less than 2 to more than 100 mg/L). Adverse effects due to intraventricular vancomycin were not confirmed. One patient, with maximum vancomycin CSF concentrations of 24.9 mg/L, experienced bilateral reduced hearing which necessitated hearing aids. Daily measurement of vancomycin CSF concentrations are suggested in patients receiving intraventricular vancomycin [16].

Pediatric FDA Approved Indications
Clostridium difficile-associated diarrhea and staphylococcal enterocolitis in pediatric patients younger than 18 years of age. **Not effective by the oral route for any other infection**[17]. Specific neonatal data were not provided by the manufacturer.

Administration

Intravenous: Administer by intermittent IV infusion over 60 to 120 minutes (**no more than 10 mg/minute**) at a concentration **not to exceed 5 mg/mL**. Concentrations up to 10 mg/mL have been used in fluid restricted patients [5]. Some institutions use standard concentrations of 5 and 10 mg/mL [6].

Extravasation Management Neonatal data are limited to pooled data from 10 case reports/case series (n=237) and are not specific to vancomycin extravasation; subcutaneous saline irrigation with or without hyaluronidase infiltration was commonly used. No standardized management was established. An option for more severe injuries (stages 3 and 4) is subcutaneous irrigation with saline, but this is not advocated as standard treatment. Conservative management is appropriate for mild extravasation (stages 1 and 2) [7]. Although not neonatal-specific, the following are recommendations for extravasation of acidic or alkaline agents (vancomycin is acidic with a pH of 4) [8]

- **General:**
- Stop and disconnect infusion; do not remove the cannula or needle
- Attempt to gently aspirate as much extravasated agent as possible; avoid manual pressure
- Remove cannula or needle
- Dry heat and elevation
- Closely monitor for signs of coagulation and ischemia
- Avoid attempt at pH neutralization (vancomycin - pH 4)
- Monitor and consider the need for surgical management such as surgical flushing with normal saline or debridement and excision of necrotic tissue (especially if pain persists for 1 to 2 weeks). In cases of compartment syndrome, surgical decompression may be required
- **Refractory Events:**
- Hyaluronidase 15 units intradermally along injection site and edematous area. Give as five, 0.2-mL intradermal injections along extravasation site and edematous tissue.
- **Inadvertent Intraarterial Administration:**
- Leave inadvertent intraarterial line in place for diagnostics
- Systemic heparin titrated to therapeutic anticoagulant effect.
- Stellate ganglion block

MEDICATION SAFETY

Contraindications/Precautions

Contraindications
Allergy to corn or corn products; premixed solution for IV use contains dextrose [33]

Precautions
Administration: Oral vancomycin is for the treatment of Clostridium difficile-associated diarrhea and staphylococcal enterocolitis and is not effective for the treatment of other types of infections. Parenteral administration of vancomycin is not an effective treatment for Clostridium difficile-associated diarrhea and staphylococcal enterocolitis [17]
Dermatologic: Severe dermatologic reactions, including toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP), and linear IgA bullous dermatosis (LABD), have been reported; discontinue treatment at first sign or symptom of TEN, SJS, DRESS, AGEP, or LABD [34]
Gastrointestinal: Use caution in patients with inflammation of intestinal mucosa due to increased risk for systemic absorption and toxicity during oral therapy; monitoring recommended in patients with renal insufficiency and/or colitis or with concomitant aminoglycoside use [35]

Hematologic: Reversible neutropenia has been reported with IV administration; monitoring recommended [5][33]
Immunologic: Overgrowth of non-susceptible bacteria may occur [17]
Infusion reactions: Infusion-related reactions, including hypotension and cardiac arrest, may occur; administer in dilute solution over at least 60 minutes and stop infusion if reaction occurs [5][33]
Infusion reactions: Thrombophlebitis may occur with IV administration [5][33]
Musculoskeletal: IM administration is associated with pain, tenderness, and necrosis [5]
Ophthalmic: Hemorrhagic occlusive retinal vasculitis, including permanent loss of vision, may occur with intracameral or intravitreal administration; safety and efficacy of intracameral or intravitreal administration has not been established [17]
Otic: Transient or permanent ototoxicity may occur especially with excessive IV doses, underlying hearing loss, or concomitant use with ototoxic agents such as aminoglycosides; monitoring recommended [35][5][33]
Renal: Nephrotoxicity, including renal failure, renal impairment, and increased blood creatinine, has been reported [35]; increased risk with underlying renal impairment or concomitant use with aminoglycosides; monitoring recommended [5][33]
Renal: Use caution in patients with renal insufficiency due to increased risk for nephrotoxicity and ototoxicity with IV administration; monitoring and dose adjustments recommended [5][33]

Adverse Effects

Nephrotoxicity and ototoxicity: May be enhanced by aminoglycoside therapy [5][36]. The overall rate of acute kidney injury (AKI) was 2.7% in a retrospective chart review in a neonatal intensive care unit (n=110; mean gestational age 29 weeks, mean birth weight 1200 g). The incidence of AKI increased with higher vancomycin trough concentrations; 1.38% for less than 10 mg/L, 0% for 10 to 15 mg/L, and 18.18% for greater than 15 mg/L [37]. The use of concurrent furosemide and vancomycin was associated with an increased risk of acute kidney injury (AKI) (adjusted OR, 3.52; 95% CI, 1.88 to 6.62) in pediatric patients (0 to 18 years of age) in the intensive care unit in a retrospective study (n=265). The rate of AKI was 23.4% [38].
Rash and hypotension (red man syndrome): Appears rapidly and resolves within minutes to hours. Lengthening infusion time usually eliminates risk for subsequent doses.
Neutropenia: Reported after prolonged administration (more than 3 weeks).
Phlebitis: May be minimized by slow infusion and dilution of the drug.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Acyclovir, alprostadil, amikacin, ampicillin, aminophylline, amiodarone, aztreonam, caffeine citrate, calcium gluconate, caspofungin, cimetidine, enalaprilat, esmolol, famotidine, fluconazole, heparin (concentrations of 1 unit/mL or less), hydrocortisone succinate, insulin, linezolid, lorazepam, magnesium sulfate, meropenem, midazolam, milrinone, morphine, nicardipine, pancuronium bromide, potassium chloride, propofol, ranitidine, remifentanil, sodium bicarbonate, vecuronium, and zidovudine.

Terminal Injection Site Incompatibility

Cefazolin, cefepime, cefotaxime, cefoxitin, ceftazidime, ceftriaxone, chloramphenicol, dexamethasone, heparin (concentrations greater than 1 unit/mL), mezlocillin, nafcillin, pentobarbital, phenobarbital, piperacillin, piperacillin/tazobactam, ticarcillin, and ticarcillin/clavulanate.

Monitoring

Auditory Function: To minimize the risk of ototoxicity, auditory function monitoring should be considered in patients receiving concomitant ototoxic drugs [18].
Laboratory Monitoring: Monitor renal function for nephrotoxicity. Periodic monitoring of white blood cell count should be done to screen for neutropenia in patients on prolonged therapy with vancomycin or those who are receiving concomitant drugs that may cause neutropenia. Monitor for infusion-related events, including hypotension and red man syndrome [5].

Vancomycin Concentration Monitoring
AUC/MIC Ratio
Suspected or serious MRSA infections: In general, target a vancomycin AUC of 400 mg x hr/L, assuming vancomycin MIC of 1 mg/L (AUC/MIC ratio of 400); may potentially target a higher AUC of 600 mg x hr/L [1].
Begin therapeutic monitoring within 24 to 48 hours of vancomycin initiation for serious MRSA infections [1]
AUC-guided monitoring is recommended for all pediatric age groups, including neonates.
Trough-only monitoring, with a target of 15 to 20 mg/L, is no longer recommended in patients with serious infections due to MRSA[1].
The optimal way to manage vancomycin dosing is through AUC-guided dosing and monitoring. Bayesian software programs for AUC monitoring with a trough concentration are recommended; however, 2 pharmacokinetic samples (ie, 1 to 2 hours post infusion and at the end of the dosing interval) may improve accuracy and precision of AUC estimates compared with using only a trough concentration. Another approach is collection of 2 concentrations (obtained near the steady-state, post-distributional peak concentration at 1 to 2 hours after infusion and trough at end of dosing interval), preferably but not required during the same dosing interval (if possible) and utilizing first-order pharmacokinetic equations to estimate the AUC [1].
Keeping the vancomycin AUC less than 800 mg x hr/L and trough less than 15 mg/mL may reduce risk of acute kidney injury [1]

Obesity: Perform early and frequent therapeutic monitoring, guided by AUC [1].
Dialysis: Obtain predialysis vancomycin serum concentrations not less than weekly; complete within 24 hours after initiating continuous renal replacement therapy [1]

Vancomycin Concentration Monitoring
Trough concentrations:
Trough-only monitoring, with a target of 15 to 20 mg/L, is no longer recommended in patients with serious infections due to MRSA[1].
Neither vancomycin troughs nor AUC have been correlated with clinical outcomes in neonates [19][20]. Multiple pharmacokinetic/pharmacodynamic studies in neonates evaluated AUC and MIC and determined vancomycin troughs of around 10 mg/L (range, 7 to 15 mg/L) for MICs of 1 mg/L or less may be adequate [21][19][22][23] for the treatment of the most common neonatal gram-positive infections, which is predominately coagulase-negative staphylococcus [24][25][26][27]. Higher troughs have been recommended in adults and children (older than neonates). For endocarditis in children (older than neonates), in the presence of MRSA with MIC of greater than 1 mg/L or when there is a lack of microbiological response, troughs of 15 to 20 mg/L may be required [10]. In adults, many experts recommend a trough of 15 to 20 mg/L when treating MRSA bacteremia, infective endocarditis, osteomyelitis, meningitis, pneumonia, complicated skin and soft-tissue infections, or bone/joint infections [28][18][29]. The recommended trough concentration range for adults with less severe infections **is 10 to 15 mg/L [18].**
For shunt infections, consider monitoring CSF vancomycin levels during therapy to assess drug concentrations (goal: trough, 5 to 10 mg/L) and potential drug accumulation [30][31][32].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action: Vancomycin is bactericidal for most gram-positive bacteria, but bacteriostatic for enterococci. It interferes with cell wall synthesis, inhibits RNA synthesis, and alters plasma membrane function. Killing activity is primarily a time-dependent process, not concentration-dependent. MICs for sensitive organisms are less than or equal to 1 mg/L.

Pharmacokinetics
Poorly absorbed orally. Diffusion into the lung and bone is variable. Minimal penetration into the CSF in absence of inflamed meninges. Protein binding is approximately 55% in adults. Mean volume of distribution is 0.3 to 0.9 L/kg in infants and 0.5 to 0.8 L/kg in children. Elimination is primarily by glomerular filtration (80% to 90% recovered unchanged in urine), with a small amount of hepatic metabolism. Higher clearance in pediatrics compared with adults (2 to 3 times higher). Mean half-life of 3 to 4 hours in infants and 2 to 3 hours in children. Not effectively removed by hemodialysis or peritoneal dialysis [5][36] [39][40].

Extracorporeal Membrane Oxygenation

A starting dose of 25 mg/kg/dose IV every 18 hours was predicted to achieve a mean AUC of 713 +/- 211 mg x hr/L and mean trough concentrations of 16.5 mg/L in neonates aged 1 to 30 days (37 to 40 weeks gestation) undergoing extracorporeal membrane oxygenation in a retrospective population pharmacokinetic simulation (n=93). The ages of patients included in the simulation were neonates 37 to 40 weeks gestation (30.1%), infants 31 days to younger than 1 year (22.6%), 1 to younger than 2 years (7.5%), 2 to 12 years of age (24.7%), and adolescents (15.1%). The mean estimated CrCl was 65 +/- 47 mL/min/1.73 m^2 for the entire pediatric population [4].

- **Parameters for neonates to adolescents (n=93):**
- **Clearance: 0.942 mL/kg/min when adjusted for 70 kg**
- **Estimated $Vd_{central}$: 0.36 L/kg**
- **Estimated $Vd_{peripheral}$: 0.462 L/kg, when adjusted for 70 kg**

Intermittent Dosing:

Initial Dose Intervals		
PMA†	**Postnatal Age†**	**Interval**
29 weeks or less	0 to 14 days older than 14 days	18 hours 12 hours
30 to 36 weeks	0 to 14 days older than 14 days	12 hours 8 hours
37 to 44 weeks	0 to 7 days older than 7 days	12 hours 8 hours
45 weeks or more	ALL	6 hours
† Postmenstrual age (PMA) is gestational age plus postnatal age. PMA is the primary determinant of dosing interval with postnatal age as the secondary qualifier.		
Renal function and drug elimination are strongly correlated with postmenstrual age.		

Trough concentrations were 10 to 20 mg/L in 60.7% and less than 10 mg/L in 39.3% of 84 initial troughs using the above dosing intervals at doses of 10 or 15 mg/kg/dose (most regimens used 10 mg/kg/dose) in a retrospective study of neonates in the intensive care unit. Of those initial troughs in the 10 to 20 mg/L range, 69.7% were 10 to 15 mg/L and 30.3% were 15 to 20 mg/L. A dose of 15 mg/kg/dose, regardless of interval, achieved a trough concentration of 10 to 20 mg/L in 74.1% of 88 neonates (97 vancomycin initial trough concentrations) [41].

The following were the vancomycin trough concentrations in neonates treated with 10 mg/kg/dose with the above dose intervals [19][42]. A trough concentration of 5 to 15 mg/L was achieved in 84.1% of neonates treated in a retrospective analysis (n=76). Only 9.3% had a trough of less than 5 mg/L [19]. Median trough concentrations were slightly above 10 mg/L for dose simulations in a retrospective population pharmacokinetic analysis. Serum trough concentrations of 5 to 15 mg/L were achieved in 52% (90% CI 43% to 60%) and

trough concentrations of 15 to 20 mg/L were achieved in 21% (90% CI 14% to 28%) [42].

Continuous Infusion: In a proposed model-based algorithm (based on postnatal age and body weight), a 10.5 mg/kg loading dose followed by 25 to 60 mg/kg/24 hours was predicted to achieve an AUC_{24}/MIC of greater than 400 when MIC was less than 1 mg/L [21]. In pharmacokinetic studies in neonates, vancomycin continuous infusion maintenance doses and target steady state concentrations were 28.3 mg/kg/day for 15 to 25 mg/L [43], 20 to 50 mg/kg/day for 15 to 25 mg/L [44][45], 30 mg/kg/day for 10 to 30 mg/L [46], and 20 to 30 mg/kg/day for 10 to 25 mg/L [47]. Some used loading doses of 10 to 20 mg/kg [43][45][46]. More infants administered continuous infusion vancomycin achieved target concentrations at the first steady-state level compared with infants administered vancomycin by intermittent infusion (85% vs 41%; p less than 0.001) in a randomized trial (n=111; mean birth weight 2271 g; mean gestational age 34 weeks, mean postnatal age 23 days). Target concentrations were 15 to 25 mg/L for continuous infusion and a trough of 10 to 20 mg/L for intermittent infusion. The mean time to target concentrations were 27.1 hours for continuous infusion and 33.6 hours for intermittent infusion [44].

ABOUT

Special Considerations/Preparation

Injection: 500-mg and 1-g vials. Reconstitute 500-mg and 1-g vial with 10 mL and 20 mL of sterile water for injection, respectively, to make a final concentration of 50 mg/mL. Reconstituted solution stable for 4 days refrigerated. Dilute prior to administration using D_5W or NS to a maximum concentration of 5 mg/mL (concentrations up to 10 mg/mL may also be used in fluid restricted patients) [5].
Powder for oral solution: 3.75 g (147 mL diluent), 7.5 g (295 mL diluent), 7.5 g (145 mL diluent), 10.5 g (203 mL diluent), and 15 g (289 mL diluent). Store prior to reconstitution refrigerated at 2 to 8 degrees C (36 to 46 degrees F). Following reconstitution, store at 2 to 8 degrees C for up to 14 days. Do not freeze. Protect from light [17].

Varicella-zoster Immune Globulin

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Prevention or Attenuation of Varicella Infection
Administer a single dose as soon as possible, **ideally within 96 hours of exposure,** for greatest effectiveness [1]. May be administered up to 10 days following exposure [2][3]. Administer a second full dose if additional exposures occur more than 3 weeks following initial dose [2][4][1].
2 kg or less: Single dose of 62.5 international units (one-half vial) IM [1].
Greater than 2 kg: Single dose of 125 international units (one vial) IM [1].

Uses

Post-exposure prophylaxis of varicella. The decision to administer varicella zoster immune globulin depends 3 factors: 1) lack of evidence of immunity, 2) whether exposure is likely to result in infection, and 3) whether the patient is at greater risk for complications than the general population. The following neonatal patients should receive varicella zoster immune globulin following exposure [2][4]:

- Immunocompromised patients
- Neonates whose mothers have signs and symptoms of varicella from 5 days before to 2 days after delivery
- Premature infants, exposed anytime during entire period for which they require hospital care for their prematurity, born at 28 weeks of gestation or greater whose mothers do not have evidence of immunity
- Premature infants, exposed anytime during entire period for which they require hospital care for their prematurity, born at less than 28 weeks of gestation or who weigh 1000 g or less at birth, regardless of maternal immunity

Varicella zoster immune globulin is not recommended for healthy, full-term infants who are exposed postnatally, even if their mothers have no history of varicella infection [4].

Any patient who received varicella zoster immune globulin to prevent varicella infection should receive varicella vaccine, unless contraindicated, at the recommended age [4].

Pediatric FDA Approved Indications
Indicated for post-exposure prophylaxis of varicella in high-risk individuals. High-risk groups include [1]:

- Premature infants
- Newborns of mothers having varicella shortly before or after delivery

- Infants less than 1 year old
- Immunocompromised patients
- Pregnant females

Administration

Administer by **IM injection only,** into the anterolateral aspects of the upper thigh. To avoid sciatic nerve injury, do not use the gluteal region for injection [1].
The final concentration of each vial is 100 international units/mL when each vial is reconstituted with **1.25 mL of diluent**[1].

MEDICATION SAFETY

Contraindications/Precautions

Contraindicated in IgA-deficient patients with antibodies against IgA and history of hypersensitivity to avoid a possible anaphylactoid reaction [1].

In patients with severe thrombocytopenia or any coagulation disorder that would contraindicate IM injection, only administer if the expected benefits outweigh the potential risks. Thrombotic events may occur; those at risk include those with multiple cardiovascular risk factors, impaired cardiac output, coagulation disorders, prolong period of immobilization, and/or know-suspected hyperviscosity [1].

Adverse Effects

The most common adverse effects observed in clinical trials and patients are injection site pain (2%) and headache (2%). Less common adverse effects include chills, fatigue, rash, and nausea [1].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Sterile preparation of purified human IgG prepared from plasma donated by healthy, screened donors with high titers of antibodies to the varicella zoster virus (VZV), the

causative agent of chickenpox. Provides passive immunization for non-immune individuals exposed to VZV, thereby reducing the severity of varicella infection. In volunteers, the mean peak concentration of varicella antibodies occurs within 5 days of administration. [1].

ABOUT

Special Considerations/Preparation

Available as a kit with a glass vial containing approximately 125 international units of freeze-dried varicella zoster virus antibodies and a single dose vial of 8.5 mL of sterile diluent. Reconstitute with only **1.25 mL of diluent** for a final concentration of 100 international units/mL. Discard the remaining sterile diluent. Store under refrigeration and do not freeze; Do not use solution that has been frozen. Do not use after expiration date. May store reconstituted solution for up to 12 hours under refrigeration prior to use. Partially used vials should also be discarded [1].

Vecuronium

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

0.1 mg/kg (0.03 to 0.15 mg/kg) IV push, as needed for paralysis. Usual dosing interval is 1 to 2 hours. Adjust dose as needed based on duration of paralysis.

Uses

Skeletal muscle relaxation/paralysis in infants requiring mechanical ventilation. Proposed desirable effects are improved oxygenation/ ventilation, reduced barotrauma, and reduced fluctuations in cerebral blood flow.

Administration

Must be accompanied by adequate analgesia and/or sedation[1].
Administer IV push over 5 to 10 seconds. For continuous IV infusion, may dilute in compatible diluent to a concentration of 0.1 to 0.2 mg/mL [1][2][3], or infuse undiluted at a concentration of 1 mg/mL.

MEDICATION SAFETY

Adverse Effects

Hypoxemia may occur because of inadequate mechanical ventilation and deterioration in pulmonary mechanics. When used alone, cardiovascular side effects are minimal; however, decreases in heart rate and blood pressure have been observed when used concurrently with narcotics.

Black Box Warning

According to the manufacturer's black box warning, vecuronium should be administered by adequately trained individuals familiar with its actions, characteristics, and hazards.

Solution Compatibility

D_5W, LR, and NS.

Terminal Injection Site Compatibility

Alprostadil, aminophylline, amiodarone, cefazolin, cimetidine, dobutamine, dopamine, epinephrine, esmolol, fentanyl, fluconazole, gentamicin, heparin, hydrocortisone succinate, isoproterenol, linezolid, lorazepam, midazolam, milrinone, morphine, nicardipine, nitroglycerin, nitroprusside, propofol, ranitidine, trimethoprim-sulfamethoxazole, and vancomycin.

Terminal Injection Site Incompatibility

Diazepam, furosemide, ibuprofen lysine, and micafungin.

Monitoring

Monitor vital signs frequently, blood pressure continuously. Use some form of eye lubrication.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Nondepolarizing muscle-relaxant that competitively antagonizes autonomic cholinergic receptors. Sympathetic stimulation is minimal. Vecuronium is metabolized rapidly in the liver to 3-desacetyl-vecuronium, which is 50% to 70% active, and is excreted renally. Newborns, particularly premature infants, are especially sensitive to vecuronium; this sensitivity diminishes with age. Onset of action is 1 to 2 minutes; duration of effect is prolonged with higher doses and in premature infants. Skeletal relaxation/paralysis is reversed by neostigmine and atropine.

Factors affecting duration of neuromuscular blockade:

Potentiation: Acidosis, hypothermia, neuromuscular disease, hepatic disease, cardiovascular disease, aminoglycosides, hypokalemia, hypermagnesemia, renal failure, and younger age.

Antagonism: Alkalosis, epinephrine, and hyperkalemia.

Sensation remains intact; analgesia should be used for painful procedures.

ABOUT

Special Considerations/Preparation

Available as powder for injection in 10-mg and 20-mg vials. Reconstitute 10 mg-vial with 10 mL of compatible solution (1 mg/mL). After reconstitution- 24 hrs stability in refrigerator. Single use only, discard unused portion. After dilution, use within 24 hours after admixing. A 0.4-mg/mL dilution may be made by diluting 1 mL of 1-mg/mL concentration with 1.5 mL of preservative-free normal saline. Dilution is stable for 24 hours in refrigerator.

DOSING/ADMINISTRATION

Dose

Vi-Sol® Multivitamin Products			
	Enfamil(R) Poly-Vi-Sol(R)	**Enfamil(R) Poly-Vi-Sol(R) with Iron**	**Enfamil(R) Tri-Vi-Sol(R)**
Vitamins	**Per 1 mL**	**Per 1 mL**	**Per 1 mL**
A (mcg RAE) (from vitamin A palmitate)	250	250	250
D (IU)	400	400	400
C (mg)	50	50	50
E (mg)	5	5	-
Thiamine (B1) (mg)	0.3	0.3	-
Riboflavin (B2) (mg)	0.4	0.4	-
Niacin (B3) (mg NE) (from niacinamide)	4	4	-
Pantothenic acid (B5) (mg)	-	-	-
B6 (mg)	0.3	0.3	-
B12 (mcg)	0.5	-	-
Folate (mcg)	-	-	-
Iron (mg) (from ferrous sulfate)	-	11	-
Key: RAE = retinol activity equivalents; NE = niacin equivalents			
https://www.hcp.meadjohnson.com/products/nutritional-supplements/enfamil-poly-vi-sol-liquid-multivitamin-supplement/ https://www.hcp.meadjohnson.com/products/nutritional-supplements/enfamil-tri-vi-sol-liquid-vitamins-a-c-and-d-supplement/ https://www.hcp.meadjohnson.com/products/nutritional-supplements/enfamil-poly-vi-sol-iron-liquid-multivitamin-supplement/			

Administration

•Place syringe tip against inside of cheek .
•A slight excess of drops will remain in syringe .
•May be slowly mixed with formula, juice, cereal or other food and fed within 1 hour .
•When added to 2 fl oz of infant formula or breast milk, the osmolality increases by 160 mOsmol /kg water with 1 mL of Poly-Vi-Sol®, 160 mOsmol /kg water with 1 mL of Poly-Vi-Sol® with iron, and 115 mOsmol/kg water with 1 mL of Tri-Vi-Sol®. If the resulting osmolality is higher than desired, an option is to add 0.5 mL of the supplement to the feeding twice per day .

DOSING/ADMINISTRATION

Dose

Intramuscular
Vitamin A Deficiency:
Less than 1 year of age: 7500 to 15,000 units IM once daily for 10 days [1].
1 to 8 years of age: 17,500 to 35,000 units IM once daily for 10 days [1].
Greater than 8 years of age: 100,000 units IM once daily for 3 days followed by 50,000 units IM once daily for 2 weeks [1].

Oral
Cystic Fibrosis - Recommended Daily Intake:
0 to 12 months of age: 1500 units/day orally [2][3].
1 to 3 years of age: 5000 units/day orally [2][3].
4 to 8 years of age: 5000 to 10,000 units/day orally [2][3].
Greater than 8 years of age: 10,000 units/day orally [2][3].

Measles Treatment:
Younger than 6 months: 50,000 units orally once daily for 2 days. Administer a third dose 2 through 4 weeks later if the child has signs and symptoms of vitamin A deficiency [4].
6 to 11 months of age: 100,000 units orally once daily for 2 days. Administer a third dose 2 through 4 weeks later if the child has signs and symptoms of vitamin A deficiency [4].
12 months or older: 200,000 units orally once daily for 2 days. Administer a third dose 2 through 4 weeks later if the child has signs and symptoms of vitamin A deficiency [4].

Vitamin A Deficiency, Follow-up Therapy After IM Treatment:
Less than 8 years of age: 5000 to 10,000 units orally once daily for 2 months [1].
8 years and older: 10,000 to 20,000 units orally once daily for 2 months [1].

Xerophthalmia:
Administer immediately on diagnosis, the next day, and 2 weeks later (3 doses total) [5].
Less than 6 months of age: 50,000 units orally [5].
6 to 12 months of age: 100,000 units orally [5].
12 months and older: 200,000 units orally [5].
Girls of reproductive age should receive up to 10,000 units orally once daily, or 25,000 units orally once weekly for 4 weeks [5].

Recommended Dietary Allowances (RDAs)/Adequate Intakes (AIs)
RDAs and AIs may both be used as goals for individual intake. RDAs are set to meet the needs of most children (97% to 98%) 1 year of age and older; AIs are used for infants 0 to 12 months of age [6].
0 to 6 months of age: AIs of 400 mcg/day [6]
7 to 12 months of age: AIs of 500 mcg/day [6]
1 to 3 years of age: RDAs of 300 mcg/day [6]

4 to 8 years: RDAs of 400 mcg/day [6]
9 to 13 years: RDAs of 600 mcg/day [6]
14 to 18 years: RDAs of 900 mcg/day (males); 700 mcg/day (females) [6]

Uses

Treatment of vitamin A deficiency. Vitamin A supplementation is appropriate for individuals or populations with vitamin A deficiency [7][2][8]. A systematic review concluded that prophylactic vitamin A supplementation in neonates in developing countries was not associated with decreased infant mortality or morbidity (eg, risk for diarrhea or respiratory tract infections) [9]. Prophylactic supplementation in infants and children was not associated with a decreased risk for respiratory infections or diarrhea, according to a meta-analysis of randomized controlled trials [8]. Routine vitamin A supplementation is not recommended [9][8].
Treatment of measles. Supplementation with vitamin A is recommended by the World Health Organization in acute measles cases, regardless of country of residence. Supplementation has been shown to decrease measles case fatality and severity of disease [4].

Administration

Do not administer IV[1].

MEDICATION SAFETY

Adverse Effects

See monitoring section for signs of toxicity. Aquasol A® Parenteral contains polysorbates, which have been associated with thrombocytopenia, renal dysfunction, hepatomegaly, cholestasis, ascites, hypotension, and metabolic acidosis in low birthweight infants [2][1].

Monitoring

Assess regularly for signs of toxicity: full fontanel, lethargy, irritability, hepatomegaly, edema, mucocutaneous lesions, and bony tenderness. Monitor serum retinol concentrations if available. Desired concentrations are approximately 30 to 70 mcg/dL. Concentrations less than 20 mcg/dL indicate deficiency. Measure serum retinyl esters as a function of total serum retinol to assess risk of toxicity, particularly in patients with malabsorption syndrome

[10][2][1].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Vitamin A is the generic name for a group of fat soluble compounds which have the biological activity of all-trans retinol. Retinol is supplied in the diet as retinyl esters. Retinol exhibits antixerophthalmic activity because it is required for the formation of rhodopsin, a pigment that is essential for normal functioning of rod cells in the retinal and dark adaptation. Vitamin A absorption requires bile salts, pancreatic lipase, and dietary fat. In malabsorption syndrome, vitamin A deficiency occurs due to reduced intraluminal bile limiting the hydrolysis of retinyl esters to retinol, and the formation of micelles, which assist absorption [7][1].

ABOUT

Special Considerations/Preparation

Available as Aquasol A® Parenteral (water-miscible vitamin A palmitate) 50,000 units per mL, equivalent to 15 mg retinol per mL, in 2-mL vials. Protect from light. Store refrigerated at 36 to 46 degrees F (2 to 8 degrees C). Do not freeze [1]. Liquid vitamin A preparations and softgel capsules for oral use are also available in various strengths and in multivitamin products.

Vitamin A activity is expressed as retinal activity equivalents (RAE); 1 RAE is equivalent to 3.3 international units of vitamin A activity (1 mcg of retinol) [1].

DOSING/ADMINISTRATION

Dose

Supplementation (for neonates exclusively breastfed or supplemented with infant formula)
Less than 2000 g: 200 to 400 international units per day orally. When weight is about 1500 g and the infant is tolerating full enteral nutrition, dose can be increased to 400 international units/day [1].
2000 g or more: 400 international units per day orally [1][2].
Treatment of vitamin D deficiency: 1000 international units per day orally.

Uses

Prevention and treatment of vitamin D deficiency: For breastfed infants, the AAP recommends that supplementation should begin within the first few days of life, regardless of whether the infant is exclusively breastfed or supplemented with infant formula. Exclusively formula-fed infants receiving at least 1000 mL/day of formula receive adequate amounts of vitamin D without supplementation [1].
Dose comparison: Median vitamin D concentrations were 22 ng/mL for placebo, 39 ng/mL for 200 international units, and 85 ng/mL for 800 international units (p less than 0.05) of oral vitamin D supplementation for 28 days in 100 newborns (23 to 27 weeks of gestation; mean weight 770 g) in a randomized, double-blinded, placebo-controlled trial. The mean number of days alive and off respiratory support at day 28 were 6.8 +/- 9.5 for placebo, 5.5 +/- 9.1 for 200 international units, and 7 +/- 10.3 for 800 international units (p=0.78) [3]. At 2 years of age, cognitive scores, neurodevelopment, language, and respiratory outcomes were not different between vitamin D and placebo (n=70). Although underpowered, 800 international units of vitamin D did not result in improvement in any outcomes at 2 years of age compared with 200 international units or placebo [4].
Some data indicate that administration of high doses of vitamin D (4000 to 6400 international units daily) to breastfeeding mothers is capable of raising 25(OH)-D levels in the infant to levels similar to those seen with infant supplementation without causing hypervitaminosis D in the mother [5][6][7].
Fortified mature human milk (24 kcal/oz) provides 283 to 379 international units/day, preterm formulas (24 kcal/oz) provide 290 to 468 international units/day, and transitional formula (22 kcal/oz) provides 125 to 127 international units/day of vitamin D in neonates (weighing more than 1500 g) with intakes of 160 mL/kg/day [1].

Rickets: In enterally fed preterm infants with radiologic evidence of rickets, maximize nutrient intake by increasing human milk fortifier and/or volume of preterm formula. If maximization cannot be tolerated, then supplementation with elemental calcium and phosphorus is recommended. Vitamin D status should be evaluated and target 25-

hydroxyvitamin D concentrations of greater than 20 ng/mL (50 nmol/L) [1].

MEDICATION SAFETY

Contraindications/Precautions

Most liquid preparations contain **propylene glycol**[9].

Adverse Effects

Signs of vitamin D toxicity include hypercalcemia, azotemia, vomiting, and nephrocalcinosis. A 25(OH)-D concentration greater than 250 nmol/L may be associated with a risk for vitamin D intoxication.

Monitoring

Signs of vitamin D deficiency include symptomatic hypocalcemia (including seizures), growth failure, irritability, lethargy, and increased susceptibility for respiratory infections. A 25-hydroxyvitamin D (25(OH)-D) concentration of less than 50 nmol/L is thought to be indicative of vitamin D deficiency in infants [2][8][5].
Biochemical monitoring of bone mineral content should be performed in very low birth weight (less than 1500 g) infants starting 4 to 5 weeks after birth [1].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

The main source of vitamin D is vitamin D_3, which is synthesized in the skin through exposure to ultraviolet B (UV-B) radiation. UV-B in the range of 290 to 315 nm initiates the synthesis of vitamin D_3 by converting 7-dehydrocholesterol into previtamin D_3, which is further converted to vitamin D_3. Vitamin D_3 binds to vitamin D-binding protein and is transported to the liver for 25-hydroxylation to 25(OH)-D (calcidiol). Calcidiol undergoes further hydroxylation in the kidney and other tissues to calcitriol (1,25-dihydroxyvitamin D) (1,25-OH_2-D), the active form of vitamin D. Calcitriol stimulates the intestinal absorption of calcium and phosphorous, renal reabsorption of filtered calcium, and mobilization of calcium and phosphorous from bone. As a supplement, vitamin D_3 has been shown to be more effective in raising 25(OH)-D levels when compared with vitamin D_2.

ABOUT

Special Considerations/Preparation

Vitamin D supplements are available as vitamin D_2 (ergocalciferol; plant derived) and vitamin D_3 (cholecalciferol; animal derived).

All liquid vitamin D_2 products contain propylene glycol . Refer to the specific manufacturer for the amount of propylene glycol [9].

•Drisdol® (ergocalciferol oral solution) contains 200 units (5 mcg) vitamin D_2 per drop. The inactive ingredient is **propylene glycol** (1036 mg/mL) [10].

•Baby D drops™ (cholecalciferol liquid vitamin supplement) is supplied as 400 units vitamin D_3 per drop. The inactive ingredient is purified palm-kernel oil.

•Bio-D-Mulsion™ (cholecalciferol; emulsified vitamin D_3) is supplied as 400 units per drop. Inactive ingredients include water, sesame oil and acacia.

•Just D (cholecalciferol) is supplied as 400 units vitamin D_3 per mL. The inactive ingredient is corn oil.

•Enfamil® D-Vi-Sol™ (cholecalciferol) is supplied as 400 units vitamin D_3 per mL. Inactive ingredients include glycerin, water, polysorbate 80, citric acid, sodium citrate, sodium hydroxide, artificial flavor and artificial caramel color.

•Aqueous Vitamin D Oral Drops (cholecalciferol) 10 mcg/mL. Contains glycerin, water and polysorbate 80 [11]

Vitamin E

NeoFax® Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Note: 1 mg alpha-tocopherol is equivalent to 1.49 international units d-alpha-tocopherol (natural) or 2.22 international units dl-alpha-tocopherol (synthetic)[1]
5 to 25 units per day orally. Dilute with feedings. Do not administer simultaneously with iron; iron absorption is impaired.

Uses

Prevention of vitamin E deficiency. May be indicated in babies receiving erythropoietin and high iron dosages. Higher doses used to reduce oxidant-induced injury (ROP, BPD, IVH) remain controversial.

MEDICATION SAFETY

Adverse Effects

Feeding intolerance may occur due to hyperosmolarity of preparation. Pharmacologic doses of alpha tocopherol have been associated with increased rates of sepsis (antioxidant effect of drug) and NEC (osmolarity of oral formulation).

Monitoring

Assess feeding tolerance. Signs of vitamin E deficiency include hemolytic anemia and thrombocytosis. Physiologic serum vitamin E concentrations are between 0.8 and 3.5 mg/dL.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Alpha-tocopherol is the most active antioxidant of the group of tocopherols known as vitamin

E. The amount required by the body is primarily dependent upon the dietary intake of fat, especially polyunsaturated fatty acids (PUFA). Human milk and currently available infant formulas contain adequate vitamin E and have appropriate E:PUFA ratios to prevent hemolytic anemia. Infants receiving supplemental iron amounts above 2 mg/kg/day may also require additional vitamin E. Oral absorption of vitamin E is dependent upon hydrolysis that requires bile salts and pancreatic esterases. This can be quite variable in very immature infants and those with fat malabsorption. Free tocopherol is absorbed in the small intestine, taken via chylomicrons into the gastrointestinal lymphatics, then carried via low-density lipoproteins to be incorporated into cell membranes. Significant tissue accumulation may occur with pharmacologic doses.

ABOUT

Special Considerations/Preparation

Availability: Aqueous vitamin E oral drops (15 mg dl-alpha tocopherol per 0.67 mL).

Tocopherol equivalents:
The natural source of vitamin E is labeled as **d-alpha-tocopherol**[1]
The synthetic source of vitamin E is labeled as **dl-alpha-tocopherol**[1]
1 mg alpha-tocopherol is equivalent to 1.49 international units d-alpha-tocopherol (natural) or 2.22 international units dl-alpha-tocopherol (synthetic) [1]
1 international unit of d-alpha tocopherol (natural) is equivalent to 0.67 mg of alpha-tocopherol [1]
1 international unit of dl-alpha tocopherol (synthetic) is equivalent to 0.45 mg of alpha-tocopherol [1]

DOSING/ADMINISTRATION

Dose

Vitamin K deficiency bleeding, Prophylaxis for early and late bleeding
Intramuscular
Preterm infants weighing 1500 g or less: 0.3 to 0.5 **mg/kg** IM within 6 hours of birth [1]
Infants weighing greater than 1500 g: 1 **mg** IM within 6 hours of birth [1]

Oral (when IM route refused)
IM is the preferred route [2][3]. *Oral route is an acceptable alternative when the IM route is refused by the parents* [4]. *Avoid the oral route in infants who are premature, ill, or unable to take oral vitamin K; have cholestasis or impaired intestinal absorption; or were exposed to drugs that interfere with vitamin K metabolism through their mothers* [2].
Guideline Dosage
2 mg orally at birth followed by 1 mg orally once weekly for 3 months [2][5]
OR 2 mg orally at birth followed by 2 mg orally at 4 to 6 days and at 4 to 6 weeks [2]
OR 2 mg orally at the first feeding followed by 2 mg orally at 2 to 4 weeks of age and 6 to 8 weeks of age [4].

Vitamin K deficiency bleeding (VKDB), Treatment:
Subcutaneous route is preferred. When IV administration is unavoidable, inject slowly (not to exceed 1 mg/minute)[6]. *Avoid IM route in the presence of coagulopathy*[7]
1 mg subQ, IM [6], or IV [6][7]. Higher doses may be necessary in infants whose mothers have been receiving oral anticoagulants [6].
In observational studies of infants with early, classical, or late VKDB, single doses of 1 to 10 mg IV were used [8][9]. Daily doses of 1 to 5 mg IV for a mean of 3.7 days have also been used [10]. .

Parenteral nutrition additive, maintenance requirement
Preterm: 10 mcg/kg/day [11]
Term: 200 mcg/day [11]

Uses

Vitamin K deficiency bleeding (VKDB); Prophylaxis for early and late bleeding (hemorrhagic disease of the newborn): The preferred route is intramuscular [4][2][13][14][5][15]. The oral route should be used only in circumstances when there are shortages of the parenteral form [5] or the injection is refused by the parents [4]. Observational studies in other countries of exclusively breast-fed infants on oral regimens identified the lowest prevalence of late VKDB with durations of vitamin K for at least 3 months [5].

Vitamin K deficiency bleeding: Bleeding resolves within a few hours after IV administration of vitamin K_1[7][16].

Pediatric FDA Approved Indications
Prophylaxis and treatment of vitamin K deficiency bleeding in neonates [6]

Administration

Intravenous
•Administer at concentrations of 1, 2, or 10 mg/mL [12] slowly **not to exceed 1 mg/minute .** [6].
•Whenever possible, administer benzyl alcohol-free formulations [6].

MEDICATION SAFETY

Contraindications/Precautions

Dermatologic: Cutaneous reactions, including eczematous reactions, scleroderma-like patches, urticaria, and delayed-type hypersensitivity reactions, have been reported with onset ranging from 1 day to a year after therapy; discontinue use if skin reactions occur [6]
Immunologic: Hypersensitivity reactions have included shock, cardiorespiratory arrest, flushing, diaphoresis, chest pain, tachycardia, cyanosis, weakness, and dyspnea and have occurred despite dilution and upon first dose [6]
Special populations: Serious adverse reactions including "gasping syndrome" have been reported in neonates and infants due to benzyl alcohol content. Consider the combined daily metabolic load of benzyl alcohol from all sources. The minimum amount of benzyl alcohol at which serious adverse reactions can occur is unknown [6].

Adverse Effects

Severe reactions, including death, have been reported with IV administration in adults. These reactions are extremely rare, and have resembled anaphylaxis and included shock and cardiac/respiratory arrest.
With IV administration, give very slowly, not exceeding 1 mg per minute, with physician present. Pain and swelling may occur at IM injection site. Efficacy of treatment with vitamin K_1 is decreased in patients with liver disease. The risk of childhood cancer is not increased by IM administration of vitamin K_1.

Black Box Warning

Warning - Hypersensitivity Reactions with Intravenous and Intramuscular use [6]

- Fatal hypersensitivity reactions, including anaphylaxis, have occurred during and immediately after intravenous and intramuscular injection of phytonadione. Reactions have occurred despite dilution to avoid rapid intravenous infusion and upon first dose. Avoid the intravenous and intramuscular routes of administration unless the subcutaneous route is not feasible and the serious risk is justified.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Amikacin, ampicillin, chloramphenicol, cimetidine, epinephrine, famotidine, heparin, hydrocortisone succinate, netilmicin, potassium chloride, ranitidine, and sodium bicarbonate.

Terminal Injection Site Incompatibility

Dobutamine and phenytoin.

Monitoring

Check prothrombin time when treating clotting abnormalities. A minimum of 2 to 4 hours is needed for measurable improvement.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Vitamin K_1 (phytonadione) promotes formation of the following clotting factors in the liver: active prothrombin (factor II), proconvertin (factor VII), plasma thromboplastin component (factor IX), and Stuart factor (factor X). Vitamin K_1 does **not** counteract the anticoagulant action of heparin [17].

ABOUT

Special Considerations/Preparation

Injection: Available as a 2 mg/mL aqueous dispersion in 0.5-mL ampules and 10 mg/mL aqueous dispersion in 1-mL ampules and 2.5- and 5-mL vials. Contains 0.9% (9 mg/mL) benzyl alcohol as a preservative. **Protect from light.**[17]
Oral: Oral formulation available as tablets containing 5 mg of phytonadione and in various strengths in multivitamin products (eg, ADEKs® drops and tablets).
Protect all phytonadione products from light and store at room temperature, 25 degrees C (77 degrees F) [18].

Extemporaneous oral solution* Efficacy associated with the use of these preparations orally is uncertain. ***

Phytonadione 1 mg/mL solution (60 mL):[19]

- Add 20 mL of sterile water for injection to an amber glass bottle.
- Withdraw 6 mL of phytonadione 10 mg/mL emulsion using a filter straw (5 micron) and add to the amber bottle.
- Add enough sterile water for injection to reach a final volume of 60 mL.
- Amber glass bottle: When refrigerated (3.7 to 4.4 degrees C), the solution was stable for 105 days.
- Amber plastic syringe as unit doses: When refrigerated (3.7 to 4.4 degrees C), the solution was stable for 14 days

Phytonadione 1 mg/mL solution (100 mL):[20]

- Mix 100 mg of phytonadione with 2 grams of Cremphor EL.
- Blend 50 mL of methylcellulose 1% solution with the phytonadione and Cremphor mixture.
- Add enough simple syrup to the mixture to reach a final volume of 100 mL.
- Package in a light-resistant container.
- Label with "Keep out of reach of children", "Use only as directed", and "Shake well"

Phytonadione 1 mg/mL solution (100 mL):[21]

- Mix 0.1 grams of phytonadione with 2 grams of cremophor EL
- Gradually add water for injection to make a clear solution then add sufficient quantity of water for injection for a final volume of 100 mL.
- To displace the oxygen, sparge nitrogen through the solution for 3 minutes.
- Filter (0.2 micro pore size, 50 mm diameter membrane) the solution.
- Sterilize oral syringes and end-cap seals by gamma irradiation.

- Aseptically fill 1 mL amber polypropylene oral syringes with the solution.
- When stored between 4 and 6 degrees C, the solution is stable for up to 6 months

DOSING/ADMINISTRATION

Dose

HIV Perinatal Prophylaxis
Oral
35 weeks gestation or longer: Initial, 4 mg/kg/dose orally every 12 hours [1].
Alternative weight band dose (birth to 4 weeks of age): 10 mg oral syrup (10 mg/mL) every 12 hours for 2 to less than 3 kg; 15 mg orally every 12 hours for 3 to less than 4 kg; and 20 mg orally every 12 hours for 4 to less than 5 kg [1].
30 weeks to less than 35 weeks gestation at birth: Initial, 2 mg/kg/dose orally every 12 hours (birth to 2 weeks postnatal age (PNA)), then 3 mg/kg/dose every 12 hours (2 weeks up to 4 to 6 weeks PNA) [1].
Less than 30 weeks gestation at birth: 2 mg/kg/dose orally every 12 hours (birth to 4 to 6 weeks postnatal age (PNA)) [1].

Intravenous (unable to tolerate oral)
35 weeks gestation or older: 3 mg/kg/dose IV every 12 hours [1].
30 to less than 35 weeks gestation: 1.5 mg/kg/dose IV every 12 hours (birth to 2 weeks postnatal age (PNA)), then 2.25 mg/kg IV every 12 hours (2 weeks up to 4 to 6 weeks PNA) [1].
Less than 30 weeks gestation: 1.5 mg/kg/dose IV every 12 hours (birth to 4 to 6 weeks postnatal age (PNA)) [1].

HIV Treatment or Empiric Therapy
Oral
35 weeks gestation or longer: Initial, 4 mg/kg/dose orally every 12 hours (birth to 4 weeks postnatal age) [1]
Alternative weight band dose (birth to 4 weeks of age): 10 mg orally of the syrup (10 mg/mL) every 12 hours for 2 to less than 3 kg; 15 mg orally every 12 hours for 3 to less than 4 kg; and 20 mg orally every 12 hours for 4 to less than 5 kg [1].
12 mg/kg/dose orally twice daily (older than 4 weeks postnatal age) [1].
30 weeks to less than 35 weeks gestation: Initial, 2 mg/kg/dose orally every 12 hours (birth to 2 weeks postnatal age (PNA)), then 3 mg/kg/dose every 12 hours (2 weeks up to 6 to 8 weeks PNA), then 12 mg/kg orally every 12 hours (older than 6 weeks to 8 weeks PNA) [1].
Less than 30 weeks gestation: Initial, 2 mg/kg/dose orally every 12 hours (birth to 4 weeks postnatal age (PNA)), then 3 mg/kg/dose every 12 hours (4 weeks up to 8 to 10 weeks PNA), then 12 mg/kg orally every 12 hours (older than 8 weeks to 10 weeks PNA) [1].

Intravenous (unable to tolerate oral)
35 weeks gestation or older: 3 mg/kg/dose IV every 12 hours (birth to 4 weeks postnatal age), then 9 mg/kg/dose orally twice daily (older than 4 weeks postnatal age) [1].
30 to less than 35 weeks gestation: 1.5 mg/kg/dose IV every 12 hours (birth to 2 weeks postnatal age (PNA)), then 2.25 mg/kg IV every 12 hours (2 weeks up to 6 to 8 weeks PNA),

then 9 mg/kg/dose IV every 12 hours (older than 6 to 8 weeks PNA) [1].
Less than 30 weeks gestation: 1.5 mg/kg/dose IV every 12 hours (birth to 4 weeks postnatal age (PNA)), then 2.25 mg/kg/dose IV every 12 hours (4 weeks up to 8 to 10 weeks PNA), then 9 mg/kg/dose IV every 12 hours (older than 8 to 10 weeks PNA) [1].

Manufacturer recommends the total daily dose divided every 6 hours for perinatal IV transmission prophylaxis and every 8 or 12 hours for HIV treatment and does not take into consideration the gestational age in their dose recommendations [2].

Uses

HIV Guidelines: [1]

Risk of HIV in Newborn	Description	Antiretroviral (ARV) Management †
Low risk of transmission	Infants 37 weeks or older gestation when the mother: • is currently receiving or has received 10 consecutive weeks of ART during pregnancy, and • has achieved and maintained or maintained viral suppression (2 consecutive tests with HIV RNA levels less than 50 copies/mL obtained at least 4 weeks apart) for the duration of pregnancy, and • has HIV RNA <50 copies/mL at or after 36 weeks and within 4 weeks of delivery, and • did not have acute HIV infection during pregnancy, and • has reported good ART	Zidovudine for 2 weeks (footnote 1)

	adherence, and adherence concerns have not been identified	
	•Infants born to mothers who do not meet the criteria above but who have HIV RNA <50 copies/mL at or after 36 weeks gestation	Zidovudine for 4 to 6 weeks (footnote 1)
	Premature infants (<37 weeks gestation) who are not at high risk of perinatal acquisition of HIV	
Higher risk of transmission	•Mother has not received antepartum or intrapartum ARV therapy, or •Mother has received only intrapartum ARV therapy, or •Mother has received antepartum and intrapartum ARV drugs but does not have viral suppression within 4 weeks prior to delivery, or •Mother has acute or primary HIV infection during pregnancy or breastfeeding (footnote 2)	Zidovudine, lamivudine, and nevirapine for 2 to 6 weeks; if duration of the 3-drug regimen is shorter than 6 weeks, zidovudine should be continued to complete 6 weeks of prophylaxis (footnote 3)
		Zidovudine, lamivudine, and raltegravir for 2 to 6 weeks; if duration of the 3-drug regimen is shorter than 6 weeks, zidovudine should be continued to complete 6 weeks of prophylaxis (footnote 3)
Presumed exposure	•Mother with unknown HIV status who test	•ARV management is the same as

	positive at delivery or postpartum, or whose newborn has positive HIV antibody test	those with higher risk of transmission (see above). •Discontinue immediately if supplemental testing confirms mother does not have HIV.
Confirmed (footnote 4)	•Confirmed positive newborn HIV virologic test/nucleic acid test	Three-drug ARV regimen using treatment doses. The preferred regimen in newborns is 2 NRTIs plus nevirapine or raltegravir

Footnotes:
1. Zidovudine prophylaxis is recommended for infants born to mothers with HIV-2 mono-infection. If mother has HIV-1 and HIV-2 co-infection, the ARV regimen should be determined based on risk. Raltegravir should be considered in patients at high risk of perinatal HIV-2 acquisition because HIV-2 is not susceptible to nevirapine
2. Most panel members opt to administer presumptive HIV therapy to infants born to mother with acute HIV infection due to the higher risk of in utero transmission. If acute HIV is diagnosed during breastfeeding, the mother should immediately discontinue breast feeding
3. The optimal duration of presumptive HIV therapy in newborns with high risk for HIV acquisition is unknown. Patients should receive the zidovudine portion of the three-drug regimen for 6 weeks. The other two ARVs (emtricitabine/nevirapine or emtricitabine/raltegravir may be administered for 2 to 6 weeks. The recommended duration of treatment with the three-drug regimen varies depends on HIV NAT results, maternal viral load at time of delivery, and additional risk factors for HIV transmission including breastfeeding
4. ART should be initiated without waiting for results of confirmatory HIV NAT testing. However, the specimen for confirmatory testing should be attained prior to ART initiation

Reference: https://clinicalinfo.hiv.gov /en/guidelines/pediatric-arv/whats-new April 2022

Antiretroviral Regimens for Initial Therapy		
Age Range	Regimen	
Preferred Regimens		
Birth to less than 14 days (footnote 1, 2)	Any weight: 2 NRTIs plus nevirapine	
	2 kg or more: 2 NRTIs plus raltegravir (footnote 3)	
14 days (and 2 kg or greater) to less than 4 weeks	2 NRTIs plus lopinavir/ritonavir (footnote 2)	
	2 NRTIs plus raltegravir (footnote 3)	
4 weeks or older (and 3 kg or greater) to less than 2 years	2 NRTIs plus dolutegravir (footnote 4)	
2 years (and 14 kg or greater) or older	2 NRTIs plus bictegravir (footnote 5)	
Alternative Regimens		
14 days to less than 3 years	2 NRTIs plus nevirapine (footnote 7)	
4 weeks to less than 3 months	Any weight: 2 NRTIs plus lopinavir/ritonavir (footnote 2)	
	2 kg or more: 2 NRTIs plus raltegravir (footnote 3)	
3 months to less than 3 years	2 NRTIs plus atazanavir/ritonavir	
	2 NRTIs plus lopinavir/ritonavir (footnote 2)	
	2 NRTIs plus raltegravir (footnote 3)	
3 years or older	2 NRTIs plus atazanavir/ritonavir	
	2 NRTIs plus darunavir/ritonavir (footnote 8)	
	2 NRTIs plus efavirenz (footnote 9)	
	2 NRTIs plus lopinavir/ritonavir (footnote 2)	
	25 kg or more	2 NRTIs plus elvitegravir/cobicistat (footnote 10)

	35 kg or more	2 NRTIs plus doravirine (footnote 11)
12 years or older with SMR 1 to 3	2 NRTIs plus one of the following: atazanavir/ritonavir, darunavir/ritonavir, efavirenz, lopinavir/ritonavir, raltegravir	
	25 kg or more	2 NRTIs plus elvitegravir/cobicistat
	35 kg or more	2 NRTIs plus one of the following: doravirine (footnote 11), rilpivirine (footnote 12), atazanavir/cobicistat
	40 kg or more	2 NRTIs plus darunavir/cobicistat
Preferred Dual NRTI Options for Use with Additional Drugs		
Birth to 1 month	abacavir plus lamivudine or emtricitabine (footnote 6)	
	zidovudine plus lamivudine or emtricitabine	
1 month to less than 2 years	abacavir plus lamivudine or emtricitabine (footnote 6)	
2 years or older and SMR 1 to 3	abacavir plus lamivudine or emtricitabine(footnote 6)	
	14 kg or greater and receiving a regimen that contains an INSTI or a NNRTI	emtricitabine/tenofovir alafenamide
	35 kg or greater and receiving a regiment that contains a boosted PI	
Alternative Dual NRTI Options for Use with Additional Drugs		
1 month to	zidovudine plus abacavir (footnote 6)	

less than 6 years	zidovudine plus lamivudine or emtricitabine
2 years to 12 years	tenofovir disoproxil fumarate plus lamivudine or emtricitabine
6 years or older and SMR 1 to 3	zidovudine plus abacavir (footnote 6)
	zidovudine plus lamivudine or emtricitabine

Footnotes:
1. Available clinical trial data do not suggest that initiating treatment within the first 14 days of life lead to better clinical outcomes than initiation after 14 days of age. Consult an expert in pediatric HIV infection before initiating in infants less than 14 days.
2. In general, lopinavir/ritonavir should not be administered to neonates before a postmenstrual age of 42 weeks and a postnatal age of 14 days or more.
3. Raltegravir film-coated tablets or chewable tablets can be used in children at least 2 years old. Consider use of the granules in infants from birth to 2 years. No dose recommendations are available for preterm infants or infants weighing less than 2 kg at birth.
4. Dolutegravir dispersible tablets can be administered in patients 4 weeks or older and 3 kg or greater. Dolutegravir film-coated tablets can be used in patients 14 kg or greater.
5. Only available as part of a fixed-dose combination tablet that contains bictegravir/emtricitabine/tenofovir alafenamide.
6. Abacavir is not approved by the FDA for use in full-term neonates and infants less than 3 months. Recent trial data from the IMPAACT P1106 trial and 2 observational cohorts provides reassurance on the safety of abacavir in patients less than 3 months. Before abacavir administration, a negative HLA-B 5701 allele test should be established
7. Do not use nevirapine in postpubertal girls if CD4 count is greater than 250/mm(3) unless clear benefit. Nevirapine is FDA-approved for infants 15 days or older.8. Darunavir should only be used in children 10 kg or more. Do not use darunavir once daily in children younger than 12 years or weighing less than 40 kg or if any one of the following resistance-associated substitutions are present: V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, and L89V.
8. Darunavir/ritonavir-boosted is an alternative recommendation for children 6 years to younger than 12 years and weighing greater than 25 kg

because there are options that can be administered once-daily and that are better tolerated. Darunavir/ritonavir-boosted administered once daily is an option for adolescents 12 years or older and weighing at least 40 kg who are not sexually mature (SMR 1 to 3) 9. Efavirenz is not recommended as initial therapy for children 3 months to 3 years (weighing at least 3.5 kg), even though it's FDA approved for this age group. Available as part of fixed-dose combination tablets 10. Elvitegravir is currently recommended only in fixed-dose combination tablets. Tablets containing elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide are an alternative for children weighing at least 25 kg due to multiple drug-drug interactions with cobicistat and a lower barrier to the development of resistance to elvitegravir 11. Doravirine is not FDA approved for pediatric use. Based on data on the efficacy and tolerability of doravirine in adults, as well as early findings from PK studies, the Panel recommends doravirine as an alternative treatment option for patients 35 kg or more 12. Rilpivirine should only be administered to adolescents 12 years or older and weighing 35 kg or more who have an initial viral load of 100,000 copies/mL or less. Available as part of a fixed-dose combination products.
INSTIs: bictegravir, dolutegravir, elvitegravir, raltegravir
NRTIs: abacavir, emtricitabine, lamivudine, tenofovir alafenamide, tenofovir disoproxil fumarate, zidovudine
NNRTIs: doravirine, efavirenz, nevirapine, rilpivirine
PIs: atazanavir, darunavir, lopinavir, ritonavir
Key: INSTI = integrase strand transfer inhibitor, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, SMR = sexual maturity rating
Reference: https://clinicalinfo.hiv.gov /en/guidelines/pediatric-arv/whats-new April 2022

Prevention of maternal-fetal HIV transmission .

In a phase III randomized trial (n=1684), the combination of 6 weeks of zidovudine plus 3 doses of nevirapine or the combination of 6 weeks of zidovudine plus nelfinavir and

lamiVUDine for 2 weeks was associated with a lower intrapartum transmission rate when compared with zidovudine alone in infants born to women who received no antenatal antiretroviral therapy (2.2% versus 2.5% versus 4.9%, respectively). The zidovudine/nelfinavir/lamiVUDine regimen was associated with increased toxicity (eg, neutropenia) [6].

Administration

Oral:
•Can be given without regard to food [2].
•Measure syrup with an appropriate-sized syringe with 0.1-mL graduation to ensure accuracy [3].
Intravenous:
•Administer IV at a constant rate over 1 hour at a **concentration not greater than 4 mg/mL**.
•Rapid infusion or bolus injection should be avoided.
• **Should not be given intramuscularly**[2].
•Recommended concentration for IV administration is 4 mg/mL [4].

The National Institute for Occupational Safety and Health (NIOSH) recommends the use of single gloves by anyone handling intact capsules or administering from a unit-dose package [5].
In the preparation of capsules, NIOSH recommends the use of double gloves and a protective gown. Prepare in a ventilated control device, if possible. Use respiratory protection if not prepared in a control device. During administration, wear single gloves, and wear eye/face protection if the formulation is hard to swallow or if the patient may resist, vomit, or spit up [5].
NIOSH recommends the use of double gloves and a protective gown by anyone handling a hazardous oral liquid or any hazardous drug via a feeding tube. Prepare in a control device, if possible. Use respiratory, eye, and face protection if not done in a control device. During administration, eye/face protection is needed if the patient may resist, or if there is potential to vomit or spit up [5].
In the preparation and administration of injections, NIOSH recommends the use of double gloves and a protective gown. Prepare in a biological safety cabinet or a compounding aseptic containment isolator; eye/face and respiratory protection may be needed. Prepare compounds in a closed system drug transfer device. During administration, if there is a potential that the substance could splash or if the patient may resist, use eye/face protection. Administer certain dosage forms via a closed system drug transfer device [5].

MEDICATION SAFETY

Contraindications/Precautions

PRECAUTIONS

Coinfection (HIV-1 and hepatitis C virus): Hepatic decompensation, some cases fatal, has been reported in patients receiving combination antiretroviral therapy and interferon alfa with or without ribavirin; monitoring recommended; discontinuation of zidovudine or dose reduction or discontinuation of interferon alfa or ribavirin may be required [9].
Concomitant Use: Avoid concomitant use with doxorubicin or stavudine [9].
Concomitant Use: Concomitant use with ribavirin is not recommended [9].
Endocrine and metabolic: Lactic acidosis, including fatal cases, has been reported with nucleoside analog use, including zidovudine; most cases occurred in women and risk factors include female sex and obesity; suspend treatment if suspected [10]
Endocrine and metabolic: Lipoatrophy has been reported and is most evident in the face, limbs, and buttocks; monitoring recommended and use of alternative treatment regimens may be warranted [10].
Hematologic: Hematologic toxicity, including reports of neutropenia, severe anemia, and pancytopenia have occurred; increased risk with dose and duration of therapy and especially in patients with advanced HIV disease; monitoring recommended; dose adjustments, interruption, discontinuation and/or blood transfusions may be necessary[9]
Hematologic: Bone marrow compromise (granulocyte count less than 1000 cells/mm(3) or hemoglobin less than 9.5 g/dL) is associated with an increased risk for hematologic toxicities; monitoring recommended; dose adjustments or discontinuation may be necessary [9].
Hepatic: Hepatic impairment; increased risk for hematologic toxicities; monitoring recommended [9].
Hepatic: Severe hepatomegaly with steatosis, including fatal cases, have been reported with nucleoside analog use, including zidovudine; most cases occurred in women and risk factors include female sex and obesity; suspend treatment if suspected; use with caution in patients with known risk factors for liver disease [10].
Immunologic: Autoimmune disorders (eg, Graves disease, polymyositis, Guillain-Barré syndrome) have been reported in the setting of immune reconstitution syndrome; onset is variable and may occur several months after treatment initiation [9].
Immunologic: Immune reconstitution syndrome has been reported; patients may develop inflammatory response to residual opportunistic infections during initial antiretroviral treatment phase; further evaluation and treatment may be necessary [9].
Latex Allergy: Zidovudine injection vial stopper contains dry natural rubber latex (a latex derivative) which could cause hypersensitivity reaction in latex-allergic patients [10].
Musculoskeletal: Symptomatic myopathy and myositis has been associated with prolonged use of zidovudine [9].
Renal: Dose reduction recommended in patients with severe renal impairment (CrCl less than 15 mL/min)[9].

Adverse Effects

Anemia and neutropenia occur frequently, and are associated with serum concentrations greater than 3 micromol/L [11]. Mild cases usually respond to a reduction in dose . Severe cases may require cessation of treatment and/or transfusion. Bone marrow toxicity may be increased by concomitant administration of acyclovir, ganciclovir, and sulfamethoxazole/trimethoprim. Transient lactic acidemia is common in infants exposed to in utero highly active antiretroviral therapy or neonatal zidovudine [12]. Concomitant treatment with fluconazole or methadone significantly reduces zidovudine metabolism - dosing interval

should be prolonged.

Lactic acidosis: Lactic acidosis has been reported with zidovudine use. Consider discontinuing ARV drugs temporarily in patients with a lactate 2.1 to 5 mmol/L (confirmed with second test) while conducting additional diagnostic work-up. In patients with a lactate 5 mmol/L or greater (confirmed with second test) or 10 mmol/L (any one test), discontinue all ARV drugs and provide supportive therapy (eg, IV fluids, sedation, respiratory support). Following resolution of clinical and laboratory abnormalities, resume therapy with either an NRTI-sparing regimen or a revised NRTI-containing regimen. Monitor lactate monthly for 3 months or more [8].
Pancreatitis: Pancreatitis has been reported with the use of NRTIs and ritonavir-boosted PIs; discontinue the offending agent and avoid reintroduction [8].
Serious skin reactions: Stevens-Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme major has been reported with lopinavir/ritonavir use. Discontinue all ARV drugs and other possible causative agents if confirmed. Provide intense supportive care, including IV hydration, aggressive wound care, eye care, labial adhesion preventative care, pain management, and antipyretics. Parenteral nutrition and antibiotics may also be needed. Consult with a specialist to determine if corticosteroids and/or IVIG is appropriate. Do not reintroduce the offending medication [8].

Black Box Warning

Zidovudine has been associated with hematologic toxicity, including neutropenia and severe anemia, particularly in patients with advanced HIV disease. Prolonged use of zidovudine has been associated with symptomatic myopathy. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur [2].

Solution Compatibility

D_5W and NS.

Terminal Injection Site Compatibility

Acyclovir, amikacin, amphotericin B, aztreonam, cefepime, ceftazidime, ceftriaxone, cimetidine, clindamycin, dexamethasone, dobutamine, dopamine, erythromycin lactobionate, fluconazole, gentamicin, heparin, imipenem, linezolid, lorazepam, metoclopramide, morphine, nafcillin, oxacillin, piperacillin, piperacillin-tazobactam, potassium chloride, ranitidine, remifentanil, tobramycin, trimethoprim-sulfamethoxazole, and vancomycin.

Terminal Injection Site Incompatibility

Meropenem.

Monitoring

Prevention of maternal-fetal HIV transmission
Initial Neonatal Management: Obtain a baseline CBC with differential; timing of followup monitoring depends on numerous exposure risks. Recheck hemoglobin and neutrophil counts 4 weeks after initiation of prophylaxis for infants who receive combination zidovudine/lamiVUDine-containing antiretroviral prophylaxis regimens [7].

Treatment of HIV infection
[8]

Antiretroviral Monitoring in Children (adjust schedule based on the specific antiretroviral regimen)							
	Entry into Care†	ART Initiation ††	1 to 2 weeks after initiation	2 to 4 weeks after initiation	Every 3 to 4 months †††	Every 6 to 12 months ‡	Virologic Failure (Prior to switching ARV regimen)
	If clinical, immunologic, or virologic deterioration is suspected, perform more frequent CD4 cell count and plasma viral load monitoring. If toxicity noted, perform testing more frequently until toxicity resolved						
Medical History and Physical Examination ‡‡, ‡‡‡	X	X	X	X	X		X
Adherence Evaluation ‡‡‡		X	X	X	X		X
CBC with differential †††	X	X		X	X		X
Chemistries †††, ♦♦	X	X		X	X		X
Lipid Panel ‡	X	X				X	
Random Plasma Glucose ♦♦♦		X				X	
Urinalysis	X	X				X	

CD4 count	X	X			X		X
Plasma Viral Load ♦	X	X		X	X		X
Resistance Testing	X						X
Hepatitis B screening ¶	X						X
Pregnancy Test for Girls and Young Women of Childbearing Potential	X	X					X
HLA-B*5701 ¶¶	X						

KEY: ARV = Antiretroviral; ART = Antiretroviral therapy; CBC = complete blood count

† If a child does not initiate ART after receiving an HIV diagnosis, the child's CD4 count and plasma viral load should be monitored at least every 3 to 4 months.

†† If ART is initiated within 30 to 90 days of a pre-therapy laboratory result, repeat testing may not be necessary.

††† CD4 cell count, CBC, and chemistries can be monitored less frequently (every 6 to 12 months) in children and youth who are adherent to therapy and have CD4 cell count values well above the threshold for opportunistic infection risk, have sustained viral suppression, and have stable clinical status for more than 2 to 3 years. Viral load testing every 3 to 4 months is generally recommended to monitor ARV adherence.

‡ If lipids have been abnormal in the past, more frequent monitoring might be needed. For patients treated with TDF, more frequent urinalysis should be considered.

‡‡ Pay special attention to changes in weight that might occur after altering an ARV regimen. Weight gain or weight loss may occur when using some ARV drugs.

‡‡‡ Virtual visits may be appropriate at some times points, particularly for adherence assessments and for visits for established patients.

♦ Some experts monitor viral load more often (with each injection) in adolescents initiating injectable cabotegravir and rilpivirine (CAB and RPV). Viral load monitoring should be performed 4 to 8 weeks after switching to long-acting CAB and RPV. HIV-RNA also should be checked in patients with unplanned missed visits and delayed dosing of long-acting CAB and RPV. When viremia develops during long-acting therapy, resistance testing, including integrase resistance testing, should be performed. Follow-up dosing in patients with missed doses should not be delayed while waiting for viral load and resistance test results. However, regimen changes should be prompted if resistance to CAB and/or RPV is discovered.

♦♦ Refers to a comprehensive metabolic panel. Some experts perform a comprehensive panel at entry and routinely test Cr, ALT, AST, with

additional tests tailored to the history of the individual patient ♦♦♦ Random plasma glucose is collected in gray-top blood collection tube or other designated tube. Some experts would consider monitoring HgbA1C, rather than blood glucose, in children at risk for prediabetes/diabetes. ¶ Only recommended for individuals who have previously demonstrated no immunity to HBV and who are initiating a regimen that contains ARV drugs with activity against HBV (ie, lamivudine, emtricitabine, tenofovir alafenamide, or tenofovir disoproxil fumarate). ¶¶ Conduct HLA-B*5701 on entry prior to initiating abacavir if not done previously. Choose an alternative ARV drug if the patient is HLA-B*5701 positive.
Reference: https://clinicalinfo.hiv.gov/en/guidelines/pediatric-arv/whats-new April 2023

CD4 Cell Count and Percentages in Healthy Children							
	0 to 3 months	3 to 6 months	6 to 12 months	1 to 2 years	2 to 6 years	6 to 12 years	12 to 18 years
CD4 cell count (footnote 1)	2600 (1600 to 4000)	2850 (1800 to 4000)	2670 (1400 to 4300)	2160 (1300 to 3400)	1380 (700 to 2200)	980 (650 to 1500)	840 (530 to 1300)
CD4 percentage (footnote 1)	52 (35 to 64)	46 (35 to 56)	46 (31 to 56)	41 (32 to 51)	38 (28 to 47)	37 (31 to 47)	41 (31 to 52)
1. Values presented as median (10th to 90th percentile)							
Reference: https://clinicalinfo.hiv.gov/en/guidelines/pediatric-arv/whats-new April 2023							

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action: Zidovudine is a nucleoside analog that inhibits HIV replication by interfering with viral reverse transcriptase. It is converted intracellularly in several steps to a triphosphate derivative, metabolized via hepatic glucuronidation, then renally excreted [2].

Protein binding is approximately 25%. Zidovudine distributes into cells by passive diffusion and is relatively lipophilic. The CSF: plasma ratio is 0.24. The relationship between serum concentration and clinical efficacy is unclear. The oral syrup is well-absorbed, but only 65% bioavailable due to significant first-pass metabolism. The serum half-life in term newborns is 3 hours, declining to 2 hours after 2 weeks of age. In preterm infants less than 33 weeks gestation, half-life during the first two weeks of life ranges from 5 to 10 hours, decreasing to

2 to 6 hours afterward [11][13].

ABOUT

Special Considerations/Preparation

Availability: 10 mg/mL oral solution and 10 mg/mL IV solution in 20 mL single-use vial [14].

Storage

Oral Solution: Store between 15 and 25 degrees C (59 and 77 degrees F) [14].

Intravenous Solution

• Store vial between 15 and 25 degrees C (59 to 77 degrees F); protect from light [14].

• After dilution, the solution is physically and chemically stable for 24 hours at room temperature and 48 hours if refrigerated between 2 and 8 degrees C (36 and 46 degrees F) [14].

Preparation

Intravenous

• Dilute in D5W before IV administration to a concentration not exceeding 4 mg/mL [14].

• The diluted solution should be used within 8 hours if stored at 25 degrees C (77 degrees F) or 24 hours if refrigerated between 2 and 8 degrees C to minimize potential administration of a microbially contaminated solution [14].

• Zidovudine injection vial stopper contains dry natural rubber latex (a latex derivative) which could cause hypersensitivity reaction in latex-allergic patients[14]