

<b>Alert</b>	There are few data from prospective trials on the safety and efficacy of metronidazole in newborn infants.		
<b>Indication</b>	Treatment of anaerobic bacterial (including meningitis) and protozoal infections. Treatment of necrotising enterocolitis.		
<b>Action</b>	Metronidazole is bactericidal against anaerobic bacteria and an antiprotozoal agent.		
<b>Drug Type</b>	Antibacterial — nitroimidazole		
<b>Trade Name</b>	Flagyl, Metronidazole Sandoz IV Solution for infusion, DBL Metronidazole Intravenous Infusion, Metronidazole Intravenous Infusion (Baxter) Solution for infusion, Metronidazole-Claris Solution for infusion  Flagyl S Suspension		
<b>Presentation</b>	500 mg/100 mL IV solution 200 mg/5 mL Oral Suspension		
<b>Dosage/Interval</b>	IV or PO		
	Postmenstrual age/Corrected age	Loading dose	Maintenance
	< 27 weeks	15 mg/kg	7.5 mg/kg 24 hourly
	27 <sup>+0</sup> –33 <sup>+6</sup> weeks	15 mg/kg	7.5 mg/kg 12 hourly
	34 <sup>+0</sup> –40 <sup>+6</sup> weeks	15 mg/kg	7.5 mg/kg 8 hourly
	≥ 41 <sup>+0</sup> weeks	15 mg/kg	7.5 mg/kg 6 hourly
<b>Maximum daily dose</b>			
<b>Route</b>	IV or PO		
<b>Preparation/Dilution</b>	IV: Use undiluted.		
<b>Administration</b>	IV Infusion: Over 30 minutes with a syringe pump. Oral: Give <b>1 hour before feeds preferably</b> .		
<b>Monitoring</b>	Full blood count if patient is on therapy > 1 week. Liver and renal function tests.		
<b>Contraindications</b>	Hypersensitivity to metronidazole or other nitroimidazoles.		
<b>Precautions</b>	Patients with seizures or peripheral neuropathy, blood dyscrasias, renal or hepatic impairment – dose reduction may be required.		
<b>Drug Interactions</b>	Co-administration with phenobarbital (phenobarbitone) and phenytoin may reduce metronidazole concentrations and increase phenytoin concentrations. Monitor anticonvulsant concentrations. Concurrent use with QT-prolonging drugs may result in increase of QT interval resulting in arrhythmias (torsades de pointes).		
<b>Adverse Reactions</b>	More common: GI upset, stomatitis and candida overgrowth. Drug metabolite may cause brownish discolouration of urine. Rare: Convulsive seizures and peripheral neuropathy characterised mainly by numbness or paraesthesia of an extremity have been reported in adults. May cause reversible leucopenia and/or thrombocytopenia.		
<b>Compatibility</b>	Fluids: Glucose 5%, glucose 10%, sodium chloride 0.9% Drugs via Y-site: Amino acid solution, aciclovir, dopamine, esmolol, fluconazole, labetalol, lipid emulsion, magnesium sulfate, methylprednisolone sodium succinate, midazolam, morphine sulfate, piperacillin-tazobactam (EDTA-free), remifentanyl		
<b>Incompatibility</b>	Amphotericin, aztreonam, cefepime, ganciclovir		
<b>Stability</b>	Once removed from original container, use as soon as practicable		
<b>Storage</b>	IV: Store below 25°C. Do NOT refrigerate. Oral suspension: Store below 25°C. Protect from light.		
<b>Special Comments</b>	Metronidazole oral suspension is best absorbed on an empty stomach.		

<b>Evidence summary</b>	<p><b>Efficacy and Safety</b></p> <p>There is a lack of data from prospective trials on the safety and efficacy of metronidazole in newborn infants. A retrospective study reported broad-spectrum antibiotics plus metronidazole may not prevent the deterioration of NEC in full-term and near-term infants.<sup>1</sup> (LOE III-3 GOR D)</p> <p><b>Pharmacokinetics</b></p> <p>Metronidazole principally undergoes hepatic metabolism with clearance increasing with weight and post-menstrual age (PMA). Cohen-Wolkowicz et al evaluated the pharmacokinetics of metronidazole in 32 infants born at <math>\leq 32</math> weeks' gestation and less than 120 days old. The study correlated metronidazole clearance with PMA and developed a PK model using nonlinear mixed-effect modeling (NONMEM). Monte Carlo simulations were performed and the study gives dosing recommendations based on PMA separated into <math>&lt; 34</math> weeks, 34 weeks to 40 weeks, and <math>&gt; 40</math> weeks.<sup>2,3</sup> Suyagh et al evaluated the pharmacokinetics of 32 infants born at <math>\leq 37</math> weeks gestation and less than 55 days old. A 1-compartment model was developed using NONMEM. Monte Carlo simulations were performed and dose recommendations are given based on PMA separated into <math>&lt; 26</math> weeks, 26–27 weeks, 28–33 weeks, and <math>\geq 34</math> weeks.<sup>4</sup> (LOE IV GOR C)</p>
<b>References</b>	<ol style="list-style-type: none"> <li>1. Luo LJ, Li X, Yang KD, Lu JY, Li LQ. Broad-spectrum antibiotic plus metronidazole may not prevent the deterioration of necrotizing enterocolitis from stage II to III in full-term and near-term infants: A propensity score-matched cohort study. <i>Medicine</i>. 2015;94(42).</li> <li>2. Cohen-Wolkowicz M, Ouellet D, Smith PB, et al. Population pharmacokinetics of metronidazole evaluated using scavenged samples from preterm infants. <i>Antimicrob Agents Chemother</i> 2012;56:1828–37.</li> <li>3. Cohen-Wolkowicz M, Sampson M, Bloom BT, et al. Determining population and developmental pharmacokinetics of metronidazole using plasma and dried blood spot samples from premature infants. <i>Pediatr Infect Dis J</i> 2013;32:956–61.</li> <li>4. Suyagh M, Collier PS, Millership JS, Iheagwaram G, Millar M, Halliday HL, McElnay JC. Metronidazole population pharmacokinetics in preterm neonates using dried blood-spot sampling. <i>Pediatrics</i>. 2011 Feb 1;127(2):e367-74.1.</li> <li>5. MIMS Product Information (2014) DBL Metronidazole Intravenous Infusion, Hospira</li> <li>6. Australian Injectable Drugs Handbook, 6th Edition 2016.</li> <li>7. Micromedex. Metronidazole monograph, accessed on 10/10/2016</li> <li>8. MIMS Product Information (2016) Flagyl S Suspension, Sanofi-Aventis</li> </ol>

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