Flucloxacillin
Newborn use only

2020

<table>
<tr><td>Alert</td><td>S4 High risk medicine.
Antimicrobial Stewardship Team listed this drug as unrestricted.</td></tr>
<tr><td>Indication</td><td>Treatment of sepsis where infection by Staphylococcus aureus or susceptible coagulase-negative Staphylococci (CoNS) is suspected or confirmed, and other infections caused by susceptible organisms.</td></tr>
<tr><td>Action</td><td>Bactericidal agent that works by inhibiting the biosynthesis of cell wall mucopeptides. Flucloxacillin is stable against beta-lactamase producing Staphylococci.</td></tr>
<tr><td>Drug type</td><td>Penicillin antibiotic.</td></tr>
<tr><td>Trade name</td><td>Flucil, Flucloxacillin sodium monohydrate for injection (DBL), Flubiclox</td></tr>
<tr><td>Presentation</td><td>500 mg vial, 1000 mg vial, 125 mg/5 mL suspension, 250 mg/5 mL suspension.</td></tr>
<tr><td>Dose/interval</td><td>IV, IM or Intraosseous: 25 mg/kg/dose every 4 hours
Recommended for infants with moderate to severe infection, with Staphylococcus aureus and susceptible coagulase negative staphylococcus infections:[1]

Alternate dosing regimen: 50 mg/kg/dose

<table><tr><th>Day of life</th><th>Dosing interval</th></tr><tr><td>Days 0–7</td><td>12 hourly</td></tr><tr><td>Days 8–20</td><td>8 hourly</td></tr><tr><td>Day 21+</td><td>6 hourly</td></tr></table>
Oral: 25 mg/kg/dose
<table><tr><th>Day of life</th><th>Dosing interval</th></tr><tr><td>Days 0–7</td><td>12 hourly</td></tr><tr><td>Days 8–20</td><td>8 hourly</td></tr><tr><td>Day 21 +</td><td>6 hourly</td></tr></table></td></tr>
<tr><td>Dose adjustment</td><td>Therapeutic hypothermia: No information.
ECMO: May need increased dosing. [2]
Renal impairment: Use with caution.
Hepatic impairment: Use with caution.</td></tr>
<tr><td>Maximum dose</td><td>200 mg/kg/day</td></tr>
<tr><td>Total cumulative dose</td><td></td></tr>
<tr><td>Route</td><td>IV
IM (only if IV route not possible as intramuscular route is painful).
Intraosseous
Oral</td></tr>
<tr><td>Preparation</td><td>IV and Intraosseous
500mg vial
Add 4.6 mL of water for injection to the 500 mg vial to make 100 mg/mL solution
FURTHER DILUTE
Draw up 5 mL (500 mg of flucloxacillin) of the above solution and add 5 mL sodium chloride 0.9% to make a final volume of 10mL with a final concentration of 50 mg/mL. [3]

1g vial
Add 4.3 mL of water for injection to the 1 g vial to make 200 mg/mL solution.
FURTHER DILUTE
Draw up 2.5 mL (500 mg of flucloxacillin) of the above solution and add 7.5 mL sodium chloride 0.9% to make a final volume of 10mL with a final concentration of 50 mg/mL. [3]
IM
500 mg vial: Add 1.6 mL of water for injection, or lidocaine (lignocaine) 1% to 500mg vial to make a 250 mg/mL solution [3

1000 mg vial: Add 3.3 mL of water for injection, or lidocaine (lignocaine) 1% to the 1000 mg vial to make a 250 mg/mL solution. [3]
NOTE: DO NOT ADMINISTER LIDOCAINE (LIGNOCAINE) CONTAINING SOLUTIONS INTRAVENOUSLY</td></tr>
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Administration	**IV:** Infuse over 30 to 60 minutes. May be given as an IV injection over 3–5 minutes, however pain and phlebitis are common and can be severe. [4] **IM:** Inject slowly into a large muscle .If administering a volume greater than 1mL, divide the dose and administer at 2 different injection sites to minimise pain. **Oral:** Give 30 to 60 minutes before feeds. Shake the bottle well before measuring dose. Usually reconstituted by Pharmacy. If supplied unreconstituted, reconstitute powder for oral suspension using water for injection with the volume specified on the bottle.
Monitoring	Liver function tests if using high dose/long course or in existing hepatic impairment. Renal function as the drug is mainly renally excreted.
Contraindications	History of flucloxacillin associated jaundice or hepatic dysfunction. History of a hypersensitivity reaction to beta-lactam antibiotics e.g., penicillins.
Precautions	Use with caution in renal or hepatic impairment. Consider dosage adjustment in renal impairment. Use with caution in jaundiced or preterm infants as flucloxacillin can displace bilirubin from albumin. IM injection can cause pain and irritation – obtaining IV access as soon as possible is recommended.
Drug interactions	Aminoglycosides, including gentamicin, should not be mixed with flucloxacillin when both drugs are given parenterally as inactivation occurs. Ensure line is adequately flushed between antibiotics.
Adverse reactions	Transient diarrhoea – common with oral doses. Hypersensitivity (rare) – urticaria, fever, bronchospasm, anaphylaxis, eosinophilia. Phlebitis (much rarer than with dicloxacillin) – monitor injection site. Hepatitis and cholestatic jaundice (may occur up to several weeks after stopping), isolated cases of nephritis.
Compatibility	**Fluids:** Glucose 5%, sodium chloride 0.9%. lidocaine (lignocaine) 0.5% or 1% **Y-site:** Adrenaline (epinephrine), aminophylline, ampicillin, dexamethasone sodium phosphate, digoxin, heparin, hydrocortisone sodium succinate, potassium chloride, ranitidine, sodium bicarbonate.
Incompatibility	**Fluids:** Amino acid solutions and lipid emulsions. **Y-site:** Aminoglycosides (e.g., gentamicin), amiodarone, atropine sulfate monohydrate, benzylpenicillin, calcium gluconate monohydrate, ciprofloxacin, dobutamine, erythromycin, metoclopramide, midazolam, morphine sulfate, vancomycin.
Stability	Use immediately following reconstitution. Vial is for single use only. Reconstituted oral suspension should be discarded after 14 days.
Storage	Vial: Store below 25°C. Oral suspension: Store powder below 25°C, once reconstituted store solution at 2–8°C
Excipients	
Special comments	Powder displacement values of 500 mg and 1 g vials are 0.4 mL and 0.7 mL respectively. [5] IM administration will result in delayed peak serum concentrations compared with administration via Intravenous or Intraosseous route
Evidence	**Efficacy:** **Infants with suspected late onset sepsis:** A single small RCT in 24 infants with suspected sepsis comparing flucloxacillin 25 mg/kg 12 hourly and gentamicin 2.5 mg/kg 12 hourly versus ticarcillin-clavulanate (Timentin) 80 mg/kg 12 hourly or 8 hourly reported no difference in mortality, treatment failure or antibiotic resistance. No infant in the flucloxacillin group had a sterile site positive culture. [6] There are no RCTs of oral treatment using flucloxacillin for newborn infections including skin (impetigo) or soft tissue infections (see pharmacokinetics/pharmacodynamics). [7] Recommendation: Therapeutic Guidelines (eTG) recommends flucloxacillin 50 mg/kg 4 to 6 hourly (child). Use a 4-hourly flucloxacillin dosing interval for critically ill patients with severe sepsis or septic shock. [8] Alternate IV Dosing regimen: An alternate dosing regime in this formulary is proposed which has been recommended by British National Formulary [9] and has been commonly used in Australia without any report of lack of efficacy (personal communication). **Infants with newly diagnosed cystic fibrosis:** A small RCT in 38 infants with newly diagnosed CF [mean (range) age of diagnosis 5-7 weeks (1-14 weeks)] treated with continuous oral flucloxacillin 250 mg/day versus episodic antimicrobials as clinically indicated reported reduced clinical symptoms, reduced Staphylococcus aureus colonisation and reduced hospitalisation in the first 2 years. Continuous

	prophylactic flucloxacillin from early diagnosis of cystic fibrosis is associated with improved clinical progress during the first two years of life. [10] (LOE II, GOR C) **Pharmacokinetics / pharmacodynamics:** There has been considerable variation in dosing recommendations for neonates regarding flucloxacillin. [11] Herngren et al in 9 newborn infants (gestational age 33-41 weeks) reported flucloxacillin 50 mg/kg 12 hourly resulted in plasma concentrations substantially above MIC for Staphylococcus aureus (0.2 mg/L). The average t½ 4.6 hours in infants 33-41 weeks was inversely correlated with gestational age. Plasma protein binding 86% affected by bilirubin/albumin ratio. Bioavailability oral flucloxacillin was 48%. [12] Conversely, Pullen et al reported 235 flucloxacillin total (free + protein bound) plasma concentrations in 55 neonates (gestation 26 to 42 weeks, postnatal age 0 to 44 days). Mean flucloxacillin elimination t½ was 2.6±1.6 hours. CoNS and Staphylococcus aureus breakpoint MIC values of flucloxacillin were 0.25 and 2.0 mg/L, respectively, equivalent to a 10 fold different MIC for Staphylococcus aureus compared with Herngren et al. The dosage regimen 25 or 50 mg/kg every 8 or 12 hours did not result in effective plasma concentrations for the treatment of Staphylococcus aureus in 31%of neonates. Recommend initial dose of 25 mg/kg/4 hourly for all neonates. [1] (LOE IV GOR C). Adrianzen Vargas 2004 reported that in 11 infants undergoing cardiopulmonary bypass the mean serum concentration of flucloxacillin decreased by 42.5% and the t½ was 2.64 (±0.23) hours. [2] (LOE IV) **Oral administration:** Bioavailability oral flucloxacillin was reported to be 48% in neonates. [12] Peak plasma levels after flucloxacillin 25 mg/kg were delayed when given orally (2 hours) compared to IV, but subsequent plasma levels were adequate to achieve levels in excess of MIC of Staphylococcus aureus. [13] Lidocaine (lignocaine) has been used as diluent for IM penicillin preparations to reduce the pain at injection site. [3]
Practice points	For the treatment of Staphylococcus aureus, the recommend initial dose of 25 mg/kg/4 hourly for all neonates. [1] (LOE IV GOR C). The bioavailability oral flucloxacillin was 48% in neonates. [12] Oral flucloxacillin 25 mg/kg produced peak plasma levels after 2 hours that were adequate to achieve levels in excess of MIC of Staphylococcus aureus. [13]
References	1. Pullen J, de Rozario L, Stolk LM, Degraeuwe PL, van Tiel FH, Zimmermann LJ. Population pharmacokinetics and dosing of flucloxacillin in preterm and term neonates. Ther Drug Monit. 2006;28:351-8. 2. Adrianzen Vargas MR, Danton MH, Javaid SM, Gray J, Tobin C, Brawn WJ, Barron DJ. Pharmacokinetics of intravenous flucloxacillin and amoxicillin in neonatal and infant cardiopulmonary bypass surgery. Eur J Cardiothorac Surg. 2004;25:256-60. 3. Amir J, Ginat S, Cohen YH, Marcus TE, Keller N, Varsano I. Lidocaine as a diluent for administration of benzathine penicillin G. Pediatr Infect Dis J. 1998;17:890-3. 4. Australian Injectable Drugs Handbook, 7th Edition. https://aidh.hcn.com.au/browse/f/flucloxacillin_sodium. 5. Flucil. Product information. Accessed on 22 November 2018. 6. Miall-Allen VM, Whitelaw AG, Darrell JH. Ticarcillin plus clavulanic acid (Timentin) compared with standard antibiotic regimes in the treatment of early and late neonatal infections. Br J Clin Pract. 1988;42:273-9. 7. George A, Rubin G. A systematic review and meta-analysis of treatments for impetigo. Br J Gen Pract. 2003;53:480-7. 8. Therapeutic Guidelines. www.tg.org.au 2018. 9. Flucloxacillin. Medicines Complete. Accessed on 15 November 2018. https://www.medicinescomplete.com.acs.hcn.com.au/#/content/bnfc/_690459654?hspl=flucloxacillin. 10. Weaver LT, Green MR, Nicholson K, Mills J, Heeley ME, Kuzemko JA, Austin S, Gregory GA, Dux AE, Davis JA. Prognosis in cystic fibrosis treated with continuous flucloxacillin from the neonatal period. Arch Dis Child. 1994;70:84-9. 11. Pacifici GM. Clinical Pharmacokinetics of Penicillins, Cephalosporins and Aminoglycosides in the Neonate: A Review. Pharmaceuticals (Basel). 2010;3:2568-91.

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13. Cohen MD, Raeburn JA, Devine J, Kirkwood J, Elliott B, Cockburn F, Forfar JO. Pharmacology of some oral penicillins in the newborn infant. Arch Dis Child. 1975;50:230-4.

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