Flucloxacillin
Newborn use only

2018

Alert	The Antimicrobial Stewardship Team has listed this drug under the following category: Unrestricted.
Indication	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.
Action	Bactericidal agent that works by inhibiting the biosynthesis of cell wall mucopeptides. Flucloxacillin is stable against beta-lactamase producing stapylococci.
Drug Type	Penicillin antibiotic.
Trade Name	Flucil, Flucloxacillin sodium monohydrate for injection (DBL), Flubiclox
Presentation	500 mg vial, 1000 mg vial, 125 mg/5 mL suspension, 250 mg/5 mL suspension.
Dosage/Interval	**IV, IM or IO:** **Recommended: 25 mg/kg/dose every 4 hours[7]** **Alternate dosing regimen**: **50 mg/kg/dose. Dosing interval as below:** **Day of life** – **Dosing interval** Days 0–7 – 12 hourly Days 8–20 – 8 hourly Day 21+ – 6 hourly **Oral: 25 mg/kg/dose. Dosing interval as below:** **Day of life** – **Dosing interval** Days 0–7 – 12 hourly Days 8–20 – 8 hourly Day 21 + – 6 hourly
Route	IV IM (only if IV route not possible as intramuscular route is painful) IO Oral
Maximum Daily Dose	200 mg/kg/day
Preparation/Dilution	**IV/IO:** Add 4.6 mL of WFI to 500 mg powder for reconstitution (100 mg/mL) OR Add 9.3 mL of WFI to the 1000 mg powder for reconstitution (100 mg/mL). Draw up 2.5 mL of reconstituted solution (250 mg) and add 2.5 mL sodium chloride 0.9% to make a final volume of 5 mL with a concentration of 50 mg/mL. **IM:** Add 1.6 mL of WFI, or lidocaine (lignocaine) 1%[11] to 500mg powder for reconstitution (250 mg/mL)[13] OR Add 3.3 mL of WFI, or lidocaine (lignocaine) 1%[11] to the 1000 mg powder for reconstitution (250 mg/mL).[13] NOTE: DO NOT ADMINISTER LIDOCAINE (LIGNOCAINE) CONTAINING SOLUTIONS INTRAVENOUSLY.
Administration	IV: Infuse over 30 to 60 minutes. May be given as a IV injection over 3–5 minutes however pain and phlebitis are common and can be severe.[11]. 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	Monitor liver function tests if using high dose/long course or in existing hepatic impairment. Monitor 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. 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), atropine sulfate monohydrate, benzylpenicillin, calcium gluconate monohydrate, ciprofloxacin, dobutamine, erythromycin lactobionate, midazolam, morphine sulfate pentahydrate, 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
Special Comments	Powder displacement values of 500 mg and 1 g vials are 0.4 mL and 0.7 mL respectively.[13] IM administration will result in delayed peak serum concentrations compared with administration via Intravenous or intraosseous route
Evidence summary	**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.[1] There are no RCTs of oral treatment using flucloxacillin for newborn infections including skin (impetigo) or soft tissue infections (see pharmacokinetics/pharmacodynamics).[2] **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.[3] **Alternate IV Dosing regimen:** An alternate dosing regime in this formulary is proposed which has been recommended by British National Formulary [12] and has been commonly used in Australia without any report of lack of efficacy (anecdotal and 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 S. 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.[4] (LOE II, GOR C) **Pharmacokinetics / pharmacodynamics:** There has been considerable variation in dosing recommendations for neonates regarding flucloxacillin.[5] 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 S aureus (0.2 mg/L). The average t ½ 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%.[6] 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 t ½ was 2.6±1.6 hours. CONS and S aureus breakpoint MIC values of flucloxacillin were 0.25 and 2.0 mg/L, respectively, equivalent to a 10 fold different MIC for S 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. [7] (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 T ½ was 2.64(+/-0.23) hours.[8] (LOE IV) **Oral administration**: Bioavailability oral flucloxacillin was reported to be 48% in neonates.[6] 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 of MIC of staph aureus. [9] Lidocaine (Lignocaine) has been used as diluent for IM penicillin preparations to reduce the pain at injection site. [10]
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