AMPHOTERICIN B – AMBISOME This drug must be guardrailed

<table>
<tr><td>Trade Name</td><td>Ambisome® - liposomal amphotericin (Gilead)</td></tr>
<tr><td>Class</td><td>Polyene antifungal</td></tr>
<tr><td>Mechanism of Action</td><td>Binds to steroidal alcohols in the cell membrane of susceptible fungi, causing loss of membrane integrity and leakage of fungal cell contents.</td></tr>
<tr><td>Indications
Individual ID approval required for full treatment course</td><td>Systemic treatment of suspected or proven fungal infections.
Active against Candida species, Aspergillus, Cryptococcus.</td></tr>
<tr><td>Contraindications</td><td>History of allergy to amphotericin or any of its constituents.
Use with caution in infants with renal or hepatic impairment.</td></tr>
<tr><td>Supplied As</td><td>50 mg powder for reconstitution
Contact Pharmacy Sterile Unit (extension 80839) to make up syringes of liposomal amphotericin – see stability section</td></tr>
<tr><td>Dilution
TWO dilution steps required
Preference is to have Pharmacy prepare this drug for 7 days due to the high cost of the vials</td><td>Depending on the dose, dilution and size of the baby this drug can either be infused via the Alaris pump and be guardrailed or for smaller volumes (<10mL) via the T34 pump.

Step 1. Reconstitute the vial
<table>
<tr><th rowspan="2">Drug</th><th>Add Diluent</th><th rowspan="2">Total Volume</th><th rowspan="2">Concentration</th></tr>
<tr><th>Water for injection</th></tr>
<tr><td>50mg (dry powder)</td><td>12 mL</td><td>12.5 mL*</td><td>4 mg / mL</td></tr>
</table>
*50mg of Ambisome® powder displaces 0.5mL of water
Shake vigorously for 30 secs until the powder appears dispersed

Step 2. Further dilute the 4 mg/mL solution in step 1
<table>
<tr><th rowspan="2">Drug</th><th>Add Diluent
use the 5 micron filter provided</th><th rowspan="2">Total Volume</th><th rowspan="2">FINAL CONCENTRATION</th></tr>
<tr><th>5% dextrose</th></tr>
<tr><td>4mg = 1mL</td><td>9 mL</td><td>10 mL</td><td>0.4 mg / mL</td></tr>
</table>
See stability section below for further information on concentrations</td></tr>
</table>

Dosage	Start at 1 mg/kg once a day, then, Increase in increments of 1mg/kg/day to a maximum of 5 mg/kg/day for severe infection eg: meningitis, osteoarthritis, cryptococcus or aspergillus infection
Guardrails	Concentration: Min – 0.4 mg/mL Max – 2mg/mL Soft Alert Min: 0.5mg/kg/hr Hard Alert Max: 5mg/kg/hr Soft Alert Max: 2.5mg/kg/hr Default Setting: 1mg/kg/hr
Interval	24 hourly
Compatible With	**Solutions:** Water for injection, dextrose 5%, dextrose 10%. **Y site compatibility:** aciclovir, adrenaline, aminophylline, buprenorphine, azithromycin, cefazolin, cefoxitin, cefuroxime, clindamycin, dexamethasone, dexmedetomidine, ephedrine, fentanyl, furosemide, heparin, hydrocortisone sodium succinate, lidocaine, methylprednisolone, milrinone, octreotide, phenobarbital, phenylephrine, piperacillin tazobactam, potassium chloride, sulfamethoxazole-trimethoprim, vasopressin, voriconazole, zidovudine.
Incompatible With	0.9% sodium chloride, TPN, Lipid, and Blood products. Amikacin, ampicillin. calcium chloride, calcium gluconate, cefotaxime, ceftazidime, ciprofloxacin, digoxin, dobutamine, dopamine, erythromycin, gentamicin, imipenem cilastatin, magnesium, meropenem, metronidazole, midazolam, morphine, ondansetron, phenytoin, propranolol, sodium bicarbonate, tobramycin, vancomycin,
Administration	**IV:** Over at least 1 hour (infusing <1 hour have been associated with hyperkalaemia) **Test dose***:* Acute reactions to amphotericin are usually related to the rate of infusion. Observe the baby closely during initial doses, and slow infusion if necessary. Our rates for infusion fall into manufacturer's guidelines for a test dose. Be careful of fluid volumes in small babies (refer to dilution information) Do not use in-line filter of <1 micron gauge.
Interactions	Monitor renal function when used in combination with other nephrotoxic agents, eg: aminoglycosides, vancomycin. Caution with drugs affecting serum potassium (eg corticosteroids), potentiation of potassium-related toxicity (eg digoxin), all drugs affecting bone marrow function, non-depolarising skeletal muscle relaxants (eg pancuronium)

Monitoring	Renal and hepatic function, full blood count, potassium, magnesium
Stability	General product information says chemically stable 72 hours after reconstitution in fridge. The data current in pharmacy (2007) suggests that solutions of liposomal amphotericin in dextrose 5% at concentrations ranging between **0.4 mg/mL and 2 mg/mL** are stable for up to seven days when **made up in the pharmacy** and stored at 2- 8 ^{o}C. Fluid and glucose tolerance will need to be assessed on an individual basis. – consult pharmacist for further assistance. **Due to the change in infusion pump parameters the maximum recommended concentration for infants weighing less than 1kg is 1 mg/mL.**
Storage	Protect from direct sunlight. Powder for reconstitution is stored at room temperature. Reconstituted solution kept in the fridge 2-8^{o}C.
Adverse Reactions	Acute infusion reactions (common, especially if infused too fast) - fever, shaking, dyspnoea, GI effects, headache, hypotension. Nephrotoxicity: increased urea and creatinine (oliguria uncommon), hypokalaemia, hypomagnesaemia, renal tubular acidosis. Effects may be prolonged (months). Caution with other nephrotoxic drugs. Wide range of less common side-effects: cardiovascular, haematological (raised and depleted cell counts possible), GI, CNS, skin, musculoskeletal. Adverse effects are less frequently reported with the liposomal preparation, but trials in neonates are lacking.
Metabolism	Liposomal amphotericin has lower renal, CSF and bone marrow tissue levels than conventional preparation (animal studies). Detailed metabolic pathways not studied in humans. Highest tissue levels in liver and spleen.
Comments	Seek specialist advice before starting amphotericin and when deciding on duration of treatment. Amphotericin is sometimes used in combination with other antifungals including 5-flucytosine or fluconazole. Ensure adequate hydration while on amphotericin. In-line filters may be used with amphotericin infusions provided the pore size is ≥1micron. There is potential for cost saving if doses are drawn up in Pharmacy
References	1. Neofax 13th Edition 2000, p6-9 2. Medicines for Children RCPCH 1999, p32-5 3. Fungizone Datasheet July 1997 4. Ambisome Datasheet May 2001 5. Trissel LA, Handbook on Injectable Drugs 11th Edition, 2001. Am Society of Health Systems Pharmacists (Editors) 6. www.medsafe.govt.nz 7. Notes on Injectable Drugs 7th Edition 8. New Zealand Formulary www.nzf.org.nz

Updated By	Bevan Headley	Sept 2002
	Kirsten Simonsen	April 2003
	K Simonsen (stability data)	Nov 2003
	P Schmidt, B Robertshawe	March 2006
	B Robertshawe	Feb 2007
	A Lynn, Robertshawe	March 2008
	A Lynn, B Robertshawe, F Robertson	May 2009 (new pumps)
	A Lynn, B Robertshawe	September 2009
	A Lynn, B Robertshawe	Nov 2012 (re-order profile, two dilutions)
	A Lynn, Tony Walls (Paed ID)	July 2013 (PHARMAC update Ab approvals)
	A Lynn, M Wallenstein, B Robertshawe, A Evison	May 2020
	A Lynn, B Robertshawe	March 2023 (double dilution instructions)