BOSENTAN

Trade Name	Dr Reddy's Bosentan®
Class	Endothelin receptor antagonist
Mechanism of Action	Blocks endothelin receptors on the smooth muscle of blood vessels preventing vasoconstriction.
Indications	Pulmonary Hypertension
Contraindications	Hypotension Avoid use in patients with severe liver impairment.
Supplied As	62.5 mg and 125 mg tablets
Dilution	Disperse one 62.5 mg tablet in 10 mL of sterile water to give a solution containing **6.25 mg/L**
Dosage	Start only after discussion between the treating team and Cardiology Wear mask, gloves and eye protection when preparing the drug Start at 0.5 mg/kg/dose and incrementally increase to a maximum of 2mg/kg/dose **Note:** recommended max = 2mg/kg/dose BD seek cardiology advice if higher dose appears indicated
Guardrails	N/A
Interval	12 hourly
Administration	Oral, can be given with or without food Can be given via oro-gastric tube
Compatible With	Do not mix in the same oral syringe with any other medicine
Incompatible With	Do not mix in the same oral syringe with any other medicine
Interactions	Bosentan is metabolised by and increases the metabolic activity of CYP3A4 and CYP2C9 **Bosentan levels can be increased by other medicines** that affect CYP3A4 and CYP 2C9 eg amiodarone, carbamazepine, clarithromycin, clozapine, digoxin, erythromycin, fentanyl, fluconazole, itraconazole, nifedipine, ritonavir, **sildenafil,** theophylline, voriconazole Bosentan levels may be reduced by medicines that induce CYP3A4 eg phenobarbital, phenytoin, rifampicin. **Bosentan is predicted to reduce concentrations of medicines** metabolised by CYP 3A4 and CYP2C9 eg. amlodipine, ciclosporin, felodipine, isradipine, methadone, midazolam, nifedipine, **sildenafil,** tacrolimus, warfarin

Monitoring	Measure baseline hepatic enzymes including ALT, AST and bilirubin prior to starting treatment. Ongoing monthly monitoring is recommended during treatment for the first 4 months then 3 monthly after that. Measurement of liver function two weeks after any change in dose is also recommended. Haemoglobin and platelet count may also be considered Echo monitoring of response ANMF recommend monitoring NT-proBNP however this is not a test that is clinically available in Chch outside a research setting and normal levels in the neonate are not clearly defined.
Stability	Discard any remaining solution immediately after use.
Storage	Store tablets in an airtight container at room temperature.
Adverse Reactions	Diarrhoea, reflux, flushing, hypotension, palpitations, oedema, fainting, headache, anaemia Less common: thrombocytopaenia, neutropoenia, leucopoenia, Rare: liver toxicity (may be reversible on discontinuation) (Note transaminase elevations are reported to occur in 2.7 – 7.8% of patients mostly in the first 5 months of treatment)
Metabolism	Extensively metabolised in the liver by CYP3A4 & 2C9 1 active metabolite Time to peak concentration in neonates less than 7 days old is 7.5 – 12 hours. In paediatrics = 1-4 hours Half life 1 – 6 hours
Comments	Some hospitals overseas have an approved formula for making a 6.25 mg/mL suspension. We don't have such a formula in NZ so doses need to be extemporaneously prepared by dispersing tablets in water. If pregnant then do not handle the tablet due to its teratogenic properties seen in animal studies
References	1. www.nzf.org.nz 2. Taketomo et al Paediatric and Neonatal Dosage Handbook 19th Edition 2012 3. BNF for Children 2019 4. www.anmfonline.org 5. Neofax in www.micromedexsolutions.com
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