Bosentan

Newborn use only

2023

Alert	Reproductive hazardous (teratogenic) drug; pregnant women are not to handle the product. Risk of hepatotoxicity.
Indication	Pulmonary arterial hypertension.[1,2,3]
Action	Antagonism of vasoconstrictor effects of endothelin-1 by blocking endothelin-A- and B-receptors. Decreases both pulmonary and systemic vascular resistance.
Drug type	Endothelin receptor antagonist.
Trade name	Tracleer. Other generic brands are available.
Presentation	Oral tablet: 62.5 mg, 12 5mg. Multiple brands are available. Suspension: 6.25 mg/mL suspension made by in-house pharmacy.
Dose	0.5-2 mg/kg/dose 12 hourly.[4,5,6] Suggested regimen: Commence at 0.5 mg/kg/dose 12 hourly. Increase incrementally in consultation with neonatologist and/or cardiologist to a maximum of 2mg/kg/dose 12 hourly. (Refer to practice points section).
Dose adjustment	Therapeutic hypothermia: Limited information. ECMO: Limited information. Renal impairment: Limited information. Hepatic impairment: reduction of dose or cessation of therapy may be required.[5,6,7]
Maximum daily dose	2mg/kg/dose 12 hourly. Note: There are no benefits to increasing the dose beyond 2mg/kg/dose 12 hourly. A cardiologist should be consulted for doses higher than this.[5]
Total cumulative dose	See maximum daily dose above.
Route	Oral
Preparation	**<u>Preparations</u>** 1. Oral suspension prepared by in-house pharmacy OR 2. Oral dispersion prepared at the bedside using one 62.5 mg tablet.[8] • Do not crush the tablet. **If pregnant, don't handle the tablet.** • Use full PPE to prepare and administer dose. (Mask, gloves, and eye protection). • Remove the plunger from a 10 mL enteral syringe and place one tablet (62.5mg) into it. • Replace the plunger. • Draw up to 10 mL with water for injection into the same enteral syringe. • Place a cap on the syringe. • Allow the tablet to disperse (This may take several minutes) to make a final volume of 10 mL and the final approximate concentration of 6.25 mg/mL of bosentan. • Once fully dispersed, shake well. • Measure the dose and administer immediately. • Discard any unused portion.
Administration	With or without feed
Monitoring	Hepatic aminotransferases should be obtained prior to initiation and monthly thereafter. More frequent monitoring is recommended if enzymes are elevated. Monitor treatment response with NT-proBNP (N-terminal pro-brain natriuretic peptide) levels, especially if the drug is continued beyond the neonatal age group. Reference levels for NT-proBNP concentrations in neonates are not well established. Refer to practice points section for further information. Haemoglobin and platelet count monitoring if clinically required.
Contraindications	Hypersensitivity to bosentan or to any component of the product. Concomitant administration with cyclosporine A or glyburide (glibenclamide).
Precautions	Risk of hepatotoxicity (bosentan is not recommended in patients with moderate or severe hepatic impairment), and embryo-fetal toxicity.
Drug interactions	Bosentan is a substrate and inducer of CYP3A4 and CYP2C9. Plasma levels and clinical efficacy of either medications can be affected if co-administered with amiodarone, clarithromycin, clozapine, digoxin doxorubicin, erythromycin, fentanyl, fluconazole, itraconazole, nifedipine, ritonavir, sildenafil, tadalafil, warfarin etc.[8] Ciclosporin (contraindicated) Glibenclamide (contraindicated) Clinicians are advised to seek further advice on nature and effect of interactions with bosentan, as they may be complex.

Adverse reactions	Fluid retention, oedema may occur within weeks of initiation and may require discontinuation of therapy. Hepatic dysfunction: Some studies have reported abnormalities of liver function in 2-10% of the participants necessitating reduction in the dose or cessation of therapy. [6,7,9] Anaemia, respiratory tract infection
Compatibility	Not applicable.
Incompatibility	Not applicable.
Stability	6.25 mg/mL suspension made by in-house pharmacy is stable at room temperature or under refrigeration for 30 days.[10]
Storage	Store tablets at room temperature below 25˚C.[11] 6.25 mg/mL oral suspension made by in-house pharmacy can also be stored at room temperature below 25˚C.[19]
Excipients	Tracleer - Acesulfame potassium, aspartame (E951), calcium hydrogen, cellulose, microcrystalline, croscarmellose sodium, magnesium stearate, phosphate anhydrous, silica colloidal anhydrous, tartaric acid, and tutti frutti flavor. [11] Other brands – Refer to manufacturer's list.
Special comments	
Evidence	**Background** Pulmonary arterial hypertension in a neonate is characterised by hypoxia due to inability of the pulmonary circulation to achieve or maintain the normal pulmonary vascular resistance. The first line therapy, inhaled nitric oxide (iNO), may not have desirable effect in approximately 40% neonates necessitating use of adjunctive or alternative medications.[1,2,3] **Efficacy** **<u>Persistent Pulmonary Hypertension in Neonates (PPHN)</u>** **Adjuvant therapy** In a small multicentre randomised placebo-controlled trial involving 21 neonates born at a mean gestation of 34 weeks, 13 neonates received bosentan 2mg/kg/dose 12-hourly in addition to iNO for management of PPHN. The primary objective of the study was to assess the efficacy of Bosentan in neonates who had an incomplete response with oxygenation index (OI) > 12 to iNO therapy after at least 4 hours of continuous treatment. In this study, the time to weaning from iNO or mechanical ventilation was not different in the Bosentan and placebo arms. One infant in the Bosentan arm needed ECMO.[4] Two studies prospectively evaluated the comparative efficacy of sildenafil alone versus sildenafil and bosentan for management of PPHN in term infants.[6,12 In] one study 15 infants were randomly assigned to receive sildenafil only while 25 infants were given sildenafil and bosentan following an echocardiographic diagnosis of PPHN.[6] On Day 3 and Day 7, greater reduction in the pulmonary arterial pressure was seen in the bosentan and sildenafil group compared to the sildenafil only group. In the second study 50 infants received sildenafil only and 50 received sildenafil with bosentan for PPHN.[12] Authors noted significantly less tricuspid regurgitation in the sildenafil and bosentan group compared to the sildenafil only group. In a retrospective cohort, 40 infants born at term received bosentan monotherapy for PPHN. The mean age of infants at initiation of bosentan was 27 hours and their mean OI was 29. In 21 infants bosentan was administered in addition to iNO. A significant reduction in the OI and alveolo-arterial oxygen difference was seen as early as 2 hours after first dose of bosentan. In this study, bosentan was administered at a dose of 1mg/kg/dose 12-hourly for a mean duration of 6 days.[13,14] This study suggests that bosentan may be a safe and effective treatment to improve oxygenation in neonates with PPHN. Bosentan can be used as an adjuvant therapy with iNO and can be an alternative option in mild--moderate PPHN. **Monotherapy** Mohamed et al assessed the efficacy and safety of bosentan as a monotherapy for management of PPHN in a placebo-controlled RCT.[15] In this study, 24 neonates received bosentan (2 mg/kg/day in two divided doses) and 23 received placebo. Improvement in the OI and pulse oxygen saturation was noted from 6 hours in a significantly higher number of infants in the bosentan arm (87%) compared with the placebo arm (20%). Moreover, in the bosentan-treated group, the mean duration of mechanical ventilation was significantly lower than that of placebo group (4.3 vs 11.5 days). A systematic review involving above mentioned two RCTs concluded that there is inadequate evidence to support the use of bosentan as stand-alone therapy or as adjuvant to inhaled nitric oxide in PPHN.[16] Overall, the quality of evidence from the included studies was considered low because of the very small sample size, methodological issues and variable aetiology of the PPHN including meconium aspiration (14 out of 40), pneumonia (15 out of 40)and idiopathic pulmonary hypertension (3 out of 40).

	Pulmonary hypertension in congenital heart disease (APAH) Bosentan appears to be effective in slowing disease progression in children with pulmonary arterial hypertension associated with congenital heart disease (CHD). In one retrospective study, 59 children (mean age 9 years) received bosentan for pulmonary hypertension associated with CHD. Before commencement of bosentan treatment, WHO functional class, 6-min walk distance (6MWD) and haemodynamic data by cardiac catheterisation were determined. Bosentan was administered for a median duration of 30 months. At the 6-month assessment, the mean WHO functional class of the participants improved from 2.8 to 2.4 and the mean 6MWD increased to 312 m from 258 m. In the survivors, the improvement was maintained for up to 3 years.[7] Rosenzweig et al investigated the long-term effects of bosentan therapy in 30 children with congenital heart disease and pulmonary hypertension.[17] Cardiopulmonary hemodynamic parameters of the participants were determined by cardiac catheterization at least 8 weeks before bosentan therapy. During the mean follow up period of 9 months, the mean pulmonary artery pressure reduced by 9 mm Hg and pulmonary vascular resistance decreased by an average of 6 U/m^2. In this study, the estimated two-year survival in children who received Bosentan for management of pulmonary hypertension alone was 94-96%. **Idiopathic pulmonary hypertension (IPAH)** The Hislop and Rosenzweig retrospective cohort studies in combination, used Bosentan monotherapy in 35 children for management of IPAH.[7,17] Clinically Significant improvement was seen in the functional WHO class, exercise tolerance and cardiopulmonary hemodynamic parameters for the participants. 40% participants in the Hislop cohort and 76% participants in the Rosenzweig cohort continued Bosentan without requiring additional therapy. The survival of the participants was 94-95% at 2 years and 55-60% at 5 years. United Kingdom Service for Pulmonary Hypertension in Children cared for the 64 children with IPAH from January 2001 and October 2007. Of the 41 treatment naïve children at recruitment, 23 were given bosentan alone and 8 received bosentan with sildenafil based on haemodynamic status. Twenty-seven patients who were commenced on monotherapy progressed to dual or triple therapy after 2 years. At 5 years, 75% children survived and 57% remained transplant-free.[18] **Safety** Bosentan was generally safe and well tolerated in the study participants.[5,12,15,19] Unlike iNO, bosentan affects systemic in addition to pulmonary vasculature which may increase the need for inotropes in patients with circulatory impairment.[13,14] Some studies have reported abnormalities of liver function in 2-10% of the participants necessitating reduction in the dose or cessation of therapy.[6,7,9] Respiratory infection is often reported in adult patients on long courses of bosentan therapy. **Pharmacokinetics** Data on pharmacokinetic properties of bosentan in neonates are sparse. In adults, oral bosentan has 50% bioavailability and the steady-state concentrations are achieved within 3–5 days after multiple-dose administration. Bosentan is ~98% bound to albumin and multiple-dose administration has a volume of distribution of 30L and a clearance of 17L/h. The terminal elimination half-life (t1/2) is about 5.4 hours. Bosentan is mainly metabolized by CYP2C9 and 3A4 isoenzymes, and therefore, kidney function has a minimal influence over it.[20] In children, the geometric mean AUC_{0-24C} is reported to be 7275 h.ng/ml when administered 2mg/kg 12 hourly with high interindividual variation. In one study, the geometric mean CmaxC of bosentan in children who were dosed 2 mg/kg 12 hourly was 743 ng/ml characterised by rapid absorption, with a median tmax of 3 hours.[5,9,19]
Practice points	• The initiation of bosentan should be in consultation with neonatology and cardiology teams. • ANMF group recommends starting at low dose and increasing the dose whilst monitoring response to therapy with echocardiogram to assess tricuspid valve regurgitation, Tricuspid Annular Plane Systolic Excursion (TAPSE), eccentricity Index and end diastolic pulmonary insufficiency. • Aim to start at 0.5 mg/kg/dose 12 hourly and increase to achieve a maximum dose of 2mg/kg/dose every 12 hours. • Assess Liver function tests prior to initiation and at least one month post initiation. • Monitor treatment response with NT-proBNP (N-terminal pro-brain natriuretic peptide) levels • Monitor for systemic and peripheral oedema. • Note: Bosentan lowers circulating levels of sildenafil. • NT-proBNP is a substance made by the heart. Blood NT-proBNP concentration greater than 125 ng/L is considered abnormal and bosentan may be continued until concentration returns to normal.
References	1. Steinhorn RH. Neonatal pulmonary hypertension. Pediatr Crit Care Med. 2010 Mar;11: S79-84.

2. Abman SH. New guidelines for managing pulmonary hypertension: what the paediatrician needs to know. Curr Opin Pediatr. 2016 Oct;28(5):597-606
3. Kam CW, Ruiz FE. Opportunities and challenges of pharmacotherapy for pulmonary arterial hypertension in children. Pediatr Pulmonol. 2021 Mar;56(3):593-613.
4. Steinhorn RH, Fineman J, Kusic-Pajic A, et al. Bosentan as Adjunctive Therapy for Persistent Pulmonary Hypertension of the Newborn: Results of the Randomized Multicentre Placebo-Controlled Exploratory Trial. J Pediatr. 2016 Oct; 177:90-96. e3.
5. Berger RMF, Gehin M, Beghetti M, et al. FUTURE-3 investigators. A bosentan pharmacokinetic study to investigate dosing regimens in paediatric patients with pulmonary arterial hypertension: FUTURE-3. Br J Clin Pharmacol. 2017 Aug;83(8):1734-1744.
6. Vijay Kumar JR, Natraj Setty HS, et al. Efficacy, safety and tolerability of bosentan as an adjuvant to sildenafil and sildenafil alone in persistent pulmonary hypertension of newborn (PPHN). Interv Med Appl Sci. 2021 Jul 16;11(4):216-220.
7. Hislop AA, Moledina S, Foster H, et al. Long-term efficacy of bosentan in treatment of pulmonary arterial hypertension in children. Eur Respir J. 2011 Jul;38(1):70-7.
8. MerativeTM Micromedex® Complete IV Compatibility (electronic version). Merative, Ann Arbor, Michigan, USA. Available at: https://www.micromedexsolutions.com/ (cited: October/30/2023).
9. Beghetti M, Haworth SG, Bonnet D, et al. Pharmacokinetic and clinical profile of a novel formulation of bosentan in children with pulmonary arterial hypertension: the FUTURE-1 study. Br J Clin Pharmacol. 2009 Dec;68(6):948-55.
10. Malik A, Gorman G, Coward L, Arnold JJ. Stability of an Extemporaneously Compounded Oral Suspension of Bosentan. Hosp Pharm. 2016 May;51(5):389-95.
11. Product information. https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/TRACLEER-pi.pdf. Accessed Aug 2023.
12. Fatima N, Arshad S, Quddusi AI, Rehman A, Nadeem A, Iqbal I. Comparison of The Efficacy of Sildenafil Alone Versus Sildenafil Plus Bosentan in Newborns with Persistent Pulmonary Hypertension. J Ayub Med Coll Abbottabad. 2018 Jul-Sep;30(3):333-336.
13. Maneenil G, Thatrimontrichai A, Janjindamai W, et al. Effect of bosentan therapy in persistent pulmonary hypertension of the newborn. Pediatr Neonatol. 2018 Feb;59(1):58-64.
14. Maneenil G, Talek S, Thatrimontrichai A, et al. The use of bosentan and sildenafil as rescue therapy in persistent pulmonary hypertension of the newborn: A single center's experience, progress in Pediatric Cardiology, Volume 67, 2022, 101575, ISSN 1058-9813.
15. Mohamed WA, Ismail M. A randomized, double-blind, placebo-controlled, prospective study of bosentan for the treatment of persistent pulmonary hypertension of the newborn. J Perinatol. 2012 Aug;32(8):608-13.
16. More K, Athalye-Jape GK, Rao SC, et al. Endothelin receptor antagonists for persistent pulmonary hypertension in term and late preterm infants. Cochrane Database Syst Rev. 2016 Aug 18;2016(8):CD010531.
17. Rosenzweig EB, Ivy DD, Widlitz A, et al. Effects of long-term bosentan in children with pulmonary arterial hypertension. J Am Coll Cardiol. 2005 Aug 16;46(4):697-704
18. Moledina S, Hislop AA, Foster H, et al. Childhood idiopathic pulmonary arterial hypertension: a national cohort study. Heart. 2010 Sep;96(17):1401-6.
19. Berger RM, Haworth SG, Bonnet D, et al. FUTURE-2: Results from an open-label, long-term safety and tolerability extension study using the pediatric FormUlation of bosenTan in pUlmonary arterial hypeRtEnsion. Int J Cardiol. 2016 Jan 1; 202:52-8
20. Wang Y, Chen S, Du J. Bosentan for Treatment of Pediatric Idiopathic Pulmonary Arterial Hypertension: State-of-the-Art. Front Pediatr. 2019 Jul 23; 7:302.
21. MIMS. Bosentan. Accessed online on 26 October 2023.

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