In **systemic sclerosis** with ongoing digital ulcer disease, bosentan is given in the same doses as for pulmonary hypertension; there are no data on safety or efficacy in patients under 18 years of age.

◊ References.

1. Krum H, *et al.* The effect of an endothelin-receptor antagonist, bosentan, on blood pressure in patients with essential hypertension. *N Engl J Med* 1998; **338:** 784–90.
2. Sutsch G, *et al.* Short-term oral endothelin-receptor antagonist therapy in conventionally treated patients with symptomatic severe chronic heart failure. *Circulation* 1998; **98:** 2262–8.
3. Kenyon KW, Nappi JM. Bosentan for the treatment of pulmonary arterial hypertension. *Ann Pharmacother* 2003; **37:** 1055–62.
4. Cohen H, *et al.* Bosentan therapy for pulmonary arterial hypertension. *Am J Health-Syst Pharm* 2004; **61:** 1107–19.
5. Dingemanse J, van Giersbergen PLM. Clinical pharmacology of bosentan, a dual endothelin receptor antagonist. *Clin Pharmacokinet* 2004; **43:** 1089–1115.

Administration in children. A short-term study[1] in 19 children with pulmonary hypertension aged 3 to 15 years found that treatment with bosentan resulted in haemodynamic improvement and was well tolerated, and another small study[2] suggested that addition of bosentan allowed epoprostenol dosage to be reduced or stopped. Longer-term studies[3,4] have reported that benefit is maintained and that bosentan may have a role in children with both idiopathic pulmonary hypertension and pulmonary hypertension secondary to heart or lung disease.

Licensed product information in the UK states that the safety and efficacy of bosentan has not been substantially documented in children under the age of 12 years (some postmarketing data has subsequently been published[5]) but notes that the studies cited above used the following doses; these doses are also recommended in the *BNFC*, but for children aged 3 to 18 years:

- body-weight 10 to 20 kg: initial dose 31.25 mg once daily, increased to 31.25 mg twice daily after 4 weeks
- body-weight 20 to 40 kg: initial dose 31.25 mg twice daily, increased to 62.5 mg twice daily after 4 weeks
- body-weight over 40 kg and age 12 to 18 years: as for adults (see above)

1. Barst RJ, *et al.* Pharmacokinetics, safety, and efficacy of bosentan in pediatric patients with pulmonary arterial hypertension. *Clin Pharmacol Ther* 2003; **73:** 372–82.
2. Ivy DD, *et al.* Weaning and discontinuation of epoprostenol in children with idiopathic pulmonary arterial hypertension receiving concomitant bosentan. *Am J Cardiol* 2004; **93:** 943–6.
3. Maiya S, *et al.* Response to bosentan in children with pulmonary hypertension. *Heart* 2006; **92:** 664–70.
4. Rosenzweig EB, *et al.* Effects of long-term bosentan in children with pulmonary arterial hypertension. *J Am Coll Cardiol* 2005; **46:** 697–704.
5. Beghetti M, *et al.* Safety experience with bosentan in 146 children 2-11 years old with pulmonary arterial hypertension: results from the European Postmarketing Surveillance program. *Pediatr Res* 2008; **64:** 200–4.

Pulmonary hypertension. Pulmonary hypertension (p.1179) is a progressive and incurable disease associated with an increase in pulmonary arterial pressure. Treatment usually involves the use of vasodilators such as calcium-channel blockers or intravenous epoprostenol, but systemic effects limit their use. Patients with pulmonary hypertension have raised plasma concentrations of the potent vasoconstrictor endothelin I, and endothelin antagonists such as bosentan have therefore been tried. Studies[1,2] with oral bosentan have shown improvement in exercise tolerance and in time to clinical progression; an open study[3] showed sustained benefit with treatment for 1 year or more. However, no effect on mortality has yet been found in randomised studies, although there is some evidence[4,5] that survival may be improved. Bosentan has also been tried with epoprostenol.[6] There was a non-significant trend towards greater improvement in the group receiving both drugs compared with epoprostenol alone.

There is some evidence that bosentan may be of benefit in pulmonary hypertension associated with congenital heart disease,[7,8] including Eisenmenger syndrome,[8-10] and in pulmonary hypertension associated with HIV infection.[11] Positive results have also been reported[12-14] in chronic thromboembolic pulmonary hypertension.

1. Channick RN, *et al.* Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. *Lancet* 2001; **358:** 1119–23.
2. Rubin LJ, *et al.* Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 2002; **346:** 896–903. Correction. *ibid.*; 1258.
3. Sitbon O, *et al.* Effects of the dual endothelin receptor antagonist bosentan in patients with pulmonary arterial hypertension: a 1-year follow-up study. *Chest* 2003; **124:** 247–54.
4. McLaughlin VV, *et al.* Survival with first-line bosentan in patients with primary pulmonary hypertension. *Eur Respir J* 2005; **25:** 244–9.
5. Sitbon O, *et al.* Survival in patients with class III idiopathic pulmonary arterial hypertension treated with first line oral bosentan compared with an historical cohort of patients started on intravenous epoprostenol. *Thorax* 2005; **60:** 1025–30.
6. Humbert M, *et al.* Combination of bosentan with epoprostenol in pulmonary arterial hypertension: BREATHE-2. *Eur Respir J* 2004; **24:** 353–9.
7. Apostolopoulou SC, *et al.* Long-term oral bosentan treatment in patients with pulmonary arterial hypertension related to congenital heart disease: a 2-year study. *Heart* 2007; **93:** 350–4.
8. Diller G-P, *et al.* Long-term safety, tolerability and efficacy of bosentan in adults with pulmonary arterial hypertension associated with congenital heart disease. *Heart* 2007; **93:** 974–6.
9. Galiè N, *et al.* for the Bosentan Randomized Trial of Endothelin Antagonist Therapy-5 (BREATHE-5) Investigators. Bosentan therapy in patients with Eisenmenger syndrome: a multicenter, double-blind, randomized, placebo-controlled study. *Circulation* 2006; **114:** 48–54.
10. D'Alto M, *et al.* Long term effects of bosentan treatment in adult patients with pulmonary arterial hypertension related to congenital heart disease (Eisenmenger physiology): safety, tolerability, clinical, and haemodynamic effect. *Heart* 2007; **93:** 621–5.
11. Barbaro G, *et al.* Highly active antiretroviral therapy compared with HAART and bosentan in combination in patients with HIV-associated pulmonary hypertension. *Heart* 2006; **92:** 1164–6.
12. Hughes R, *et al.* Bosentan in inoperable chronic thromboembolic pulmonary hypertension. *Thorax* 2005; **60:** 707.
13. Hoeper MM, *et al.* Bosentan therapy for inoperable chronic thromboembolic pulmonary hypertension. *Chest* 2005; **128:** 2363–7.
14. Bonderman D, *et al.* Bosentan therapy for inoperable chronic thromboembolic pulmonary hypertension. *Chest* 2005; **128:** 2599–2603.

Scleroderma. Bosentan has an established role in pulmonary hypertension secondary to scleroderma (p.1817) or other connective tissue disorders, but may also have additional benefits. Several case reports[1-3] have suggested that treatment with bosentan may be associated with healing of refractory digital ulcers in patients with scleroderma, and a controlled study[4] found that bosentan reduced the incidence of new digital ulcers, although there was no improvement in the healing of existing ulcers. Relatively long-term treatment may need to be given.[5]

1. Humbert M, Cabane J. Successful treatment of systemic sclerosis digital ulcers and pulmonary arterial hypertension with endothelin receptor antagonist bosentan. *Rheumatology (Oxford)* 2003; **42:** 191–3.
2. Snyder MJ, *et al.* Resolution of severe digital ulceration during a course of bosentan therapy. *Ann Intern Med* 2005; **142:** 802–3.
3. Tillon J, *et al.* Successful treatment of systemic sclerosis-related digital ulcers and sarcoidosis with endothelin receptor antagonist (bosentan) therapy. *Br J Dermatol* 2006; **154:** 1000–1002.
4. Korn JH, *et al.* Digital ulcers in systemic sclerosis: prevention by treatment with bosentan, an oral endothelin receptor antagonist. *Arthritis Rheum* 2004; **50:** 3985–93.
5. García de la Peña-Lefebvre P, *et al.* Long-term experience of bosentan for treating ulcers and healed ulcers in systemic sclerosis patients. *Rheumatology (Oxford)* 2008; **47:** 464–6.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Tracleer; ***Belg.:*** Tracleer; ***Canad.:*** Tracleer; ***Cz.:*** Tracleer; ***Denm.:*** Tracleer; ***Fin.:*** Tracleer; ***Fr.:*** Tracleer; ***Ger.:*** Tracleer; ***Gr.:*** Tracleer; ***Hung.:*** Tracleer; ***Irl.:*** Tracleer; ***Israel:*** Tracleer; ***Ital.:*** Tracleer; ***Malaysia:*** Tracleer; ***Neth.:*** Tracleer; ***Norw.:*** Tracleer; ***NZ:*** Tracleer; ***Port.:*** Tracleer; ***Singapore:*** Tracleer; ***Spain:*** Tracleer; ***Swed.:*** Tracleer; ***Switz.:*** Tracleer; ***Thai.:*** Tracleer; ***UK:*** Tracleer; ***USA:*** Tracleer.

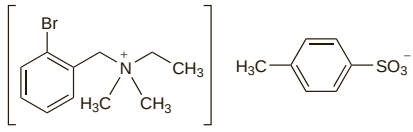
Bretylium Tosilate *(BAN, rINN)*

ASL-603; Bretyli Tosilas; Bretylii Tosilas; Brétylium, Tosilate de; Bretylium Tosylate *(USAN)*; Bretyltosilat; Bretyylitosilaatti; Tosilato de bretilio. (2-Bromobenzyl)ethyldimethylammonium toluene-4-sulphonate.

Бретилия Тозилат

$C_{11}H_{17}BrN,C_7H_7O_3S$ = 414.4.

CAS — 59-41-6 (bretylium); 61-75-6 (bretylium tosilate).
ATC — C01BD02.
ATC Vet — QC01BD02.



Pharmacopoeias. In *Br.* and *US.*

BP 2008 (Bretylium Tosilate). A white crystalline powder. M.p. about 98°. It exhibits polymorphism. Freely soluble in water, in alcohol, and in methyl alcohol. A 5% solution in water has a pH of 5.0 to 6.5. Store in airtight containers at a temperature not exceeding 25°. Protect from light.

USP 31 (Bretylium Tosylate). A white, hygroscopic, crystalline powder. Freely soluble in water, in alcohol, and in methyl alcohol; practically insoluble in ether, in ethyl acetate, and in hexane. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°.

Adverse Effects and Precautions

The most common adverse effect of bretylium is hypotension, which may be severe. Bretylium may also cause a transient initial increase in blood pressure and heart rate, and a worsening of cardiac arrhythmias due to a release of noradrenaline. Nausea and vomiting may occur particularly during rapid intravenous infusion. Intramuscular injection of bretylium can lead to local tissue necrosis and muscle atrophy. Caution is required in patients with renal impairment, and in patients with severe aortic stenosis or pulmonary hypertension in whom cardiac output may not increase in response to the fall in peripheral resistance produced by bretylium.

Interactions

Bretylium may exacerbate arrhythmias caused by digitalis toxicity and may enhance the effects of sympathomimetics.

Pharmacokinetics

Bretylium is incompletely absorbed from the gastrointestinal tract. It is well absorbed after intramuscular injection. It is not metabolised and is largely excreted unchanged in the urine. The half-life is reported to be between 4 and 17 hours in patients with normal renal function and is prolonged in patients with renal impairment. Bretylium is dialysable.

Uses and Administration

Bretylium is a quaternary ammonium compound with class II and class III antiarrhythmic activity (p.1153); it causes an initial release of noradrenaline and then blocks adrenergic transmission by preventing noradrenaline release from adrenergic nerve endings. It suppresses ventricular fibrillation and other ventricular arrhythmias, but its exact mode of action is unknown. It has been given parenterally as the tosilate in the management of ventricular arrhythmias.

Bretylium has also been investigated in complex regional pain syndrome.

Preparations

BP 2008: Bretylium Injection;
USP 31: Bretylium Tosylate in Dextrose Injection; Bretylium Tosylate Injection.

Proprietary Preparations (details are given in Part 3)
Israel: Bretylate†; ***S.Afr.:*** Bretylol†.

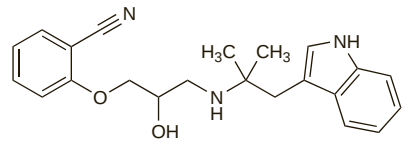
Bucindolol Hydrochloride *(BANM, USAN, rINNM)* ⊗

Bucindolol, Chlorhydrate de; Bucindololi Hydrochloridum; Hidrocloruro de bucindolol; MJ-13105-1. 2-[2-Hydroxy-3-(2-indol-3-yl-1,1-dimethylethylamino)propoxy]benzonitrile hydrochloride.

Буциндолола Гидрохлорид

$C_{22}H_{25}N_3O_2$,HCl = 399.9.

CAS — 71119-11-4 (bucindolol); 70369-47-0 (bucindolol hydrochloride).



(bucindolol)

Profile

Bucindolol is a non-cardioselective beta blocker (p.1225). It is reported to possess weak alpha$_1$-blocking activity and direct vasodilating activity; the degree of intrinsic sympathomimetic activity is unclear. Bucindolol hydrochloride has been investigated in the management of hypertension, heart failure, and other cardiac disorders, but development was halted. However, it has been suggested that it may be of benefit in a genetically identifiable subgroup of patients.

◊ References.

1. The Beta-Blocker Evaluation of Survival Trial Investigators. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. *N Engl J Med* 2001; **344:** 1659–67.

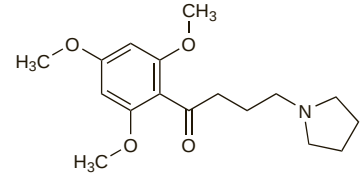
Buflomedil Hydrochloride *(BANM, rINNM)*

Buflomediilihydrokloridi; Buflomédil, chlorhydrate de; Buflomedil-hidroklorid; Buflomedil-hydrochlorid; Buflomedilhydroklorid; Buflomedili hydrochloridum; Buflomedilio hidrochloridas; Hidrocloruro de buflomedil; LL-1656. 2′,4′,6′-Trimethoxy-4-(pyrrolidin-1-yl)butyrophenone hydrochloride.

Буфломедила Гидрохлорид

$C_{17}H_{25}NO_4$,HCl = 343.8.

CAS — 55837-25-7 (buflomedil); 35543-24-9 (buflomedil hydrochloride).
ATC — C04AX20.
ATC Vet — QC04AX20.



(buflomedil)