4. Stone GW, *et al.* ACUITY Investigators. Bivalirudin for patients with acute coronary syndromes. *N Engl J Med* 2006; **355:** 2203–16.
5. Ahrens I, *et al.* Direct thrombin inhibition with bivalirudin as an antithrombotic strategy in general and interventional cardiology. *Expert Opin Drug Metab Toxicol* 2007; **3:** 609–20.
6. Hartmann F. Safety and efficacy of bivalirudin in acute coronary syndromes. *Curr Pharm Des* 2008; **14:** 1191–6.

Administration in renal impairment. The dose of bivalirudin may need to be adjusted in patients with renal impairment and the activated clotting time should be monitored. UK licensed product information recommends the following doses, depending on the glomerular filtration rate (GFR):

- GFR 30 to 59 mL/minute, usual bolus doses (see Uses and Administration, above) but in those undergoing percutaneous coronary intervention (PCI) for any indication the infusion rate should be reduced to 1.4 mg/kg per hour during the procedure
- GFR below 30 mL/minute or dialysis-dependent, contra-indicated

US licensed product information recommends the following doses for those undergoing PCI, based on creatinine clearance (CC):

- CC 30 to 59 mL/minute, usual bolus and infusion doses
- CC below 30 mL/minute, usual bolus doses but infusion rate reduced to 1 mg/kg per hour
- Haemodialysis patients, usual bolus doses but infusion rate reduced to 250 micrograms/kg per hour

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Angiomax; ***Austral.:*** Angiomax; ***Canad.:*** Angiomax; ***Cz.:*** Angiox; ***Denm.:*** Angiox; ***Fin.:*** Angiox; ***Fr.:*** Angiox; ***Ger.:*** Angiox; ***Gr.:*** Angiox; ***Hung.:*** Angiox; ***Israel:*** Angiomax; ***Ital.:*** Angiox; ***Neth.:*** Angiox; ***Norw.:*** Angiox; ***NZ:*** Angiomax; ***Port.:*** Angiox; ***Spain:*** Angiox; ***Swed.:*** Angiox; ***UK:*** Angiox; ***USA:*** Angiomax.

Bopindolol Malonate *(rINNM)* ⊗

Bopindolol Hydrogen Malonate; Bopindolol, Malonate de; Bopindololi Malonas; LT-31-200; Malonato de bopindolol. (±)-1-(*tert*-Butylamino)-3-[(2-methylindol-4-yl)oxy]propan-2-ol benzoate malonate.

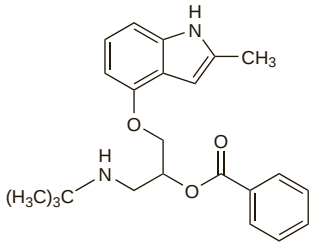
Бопиндолола Малонат

$C_{23}H_{28}N_2O_3,C_3H_4O_4$ = 484.5.

CAS — 62658-63-3 (bopindolol); 82857-38-3 (bopindolol malonate).

ATC — C07AA17.

ATC Vet — QC07AA17.



(bopindolol)

Profile

Bopindolol is a non-cardioselective beta blocker (p.1225). It is reported to possess some intrinsic sympathomimetic activity.

Bopindolol is given orally as the malonate but doses are expressed in terms of the base; 1.27 mg of bopindolol malonate is equivalent to about 1 mg of base. It is used in the management of hypertension (p.1171) and angina pectoris (p.1157) in daily doses equivalent to 0.5 to 2 mg of bopindolol.

◊ References.

1. Harron DWG, *et al.* Bopindolol: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy. *Drugs* 1991; **41:** 130–49.
2. Nagatomo T, *et al.* Bopindolol: pharmacological basis and clinical implications. *Cardiovasc Drug Rev* 2001; **19:** 9–24.

Preparations

Proprietary Preparations (details are given in Part 3)

Cz.: Sandonorm; ***Ger.:*** Wandonorm†; ***Gr.:*** Sandonorm†; ***Hung.:*** Sandonorm; ***Switz.:*** Sandonorm.

Multi-ingredient: ***Switz.:*** Sandoretic.

Bosentan *(BAN, USAN, rINN)*

Bosentaani; Bosentán; Bosentano; Bosentanum; Ro-47-0203/029. *p-tert*-Butyl-*N*-[6-(2-hydroxyethoxy)-5-(*o*-methoxyphenoxy)-2-(2-pyrimidinyl)-4-pyrimidinyl]benzenesulfonamide.

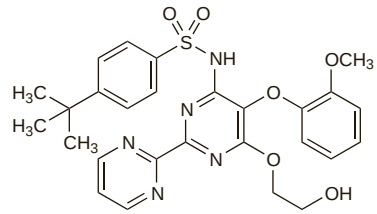
Бозентан

$C_{27}H_{29}N_5O_6S$ = 551.6.

CAS — 147536-97-8 (anhydrous bosentan); 157212-55-0 (bosentan monohydrate).

ATC — C02KX01.

ATC Vet — QC02KX01.



Adverse Effects

Adverse effects reported with bosentan include headache, nasopharyngitis, flushing, oedema, hypotension, dizziness, palpitations, gastrointestinal disturbances, pruritus, skin rashes, fatigue, muscle cramps, and anaemia. Anaphylaxis and angioedema have been reported rarely. Dose-related increases in liver aminotransferases may also occur, and hepatic cirrhosis and liver failure have been reported.

Bosentan is teratogenic in *animals*.

Effects on the liver. In a postmarketing study,[1] increases in liver aminotransferases to more than 3 times the upper limit of normal occurred in 352 (7.6%) of 4623 patients started on bosentan for pulmonary hypertension; treatment was continued or successfully reintroduced after temporary withdrawal in 165 (47%) of these patients.

1. Humbert M, *et al.* Results of European post-marketing surveillance of bosentan in pulmonary hypertension. *Eur Respir J* 2007; **30:** 338–44.

Effects on the skin. Vasculitis was reported[1] in a patient receiving bosentan shortly after the dose was increased to 125 mg twice daily. She was also taking metolazone and acenocoumarol long term, and spironolactone had recently been added. The skin lesions improved slowly over a period of weeks after bosentan was stopped. All other treatment was continued and it was concluded that the lesions were attributable to bosentan alone or to a previously unknown interaction.

1. Gasser S, *et al.* Severe necrotising leucocytoclastic vasculitis in a patient taking bosentan. *BMJ* 2004; **329:** 430.

Precautions

Bosentan is contra-indicated in patients with moderate to severe hepatic impairment (Child-Pugh Class B or C). Liver-aminotransferase concentrations should be measured before starting therapy, at monthly intervals during therapy, and 2 weeks after any increase in dose:

- bosentan therapy should not be *started* in patients with concentrations more than 3 times the upper limit of normal
- if concentrations increase to between 3 and 5 times the upper limit of normal *during* treatment, bosentan should be stopped or the dose reduced and concentrations should be monitored every 2 weeks until they are below the pretreatment value; therapy may then be continued or reintroduced, but aminotransferase concentrations should be checked after 3 days, after a further 2 weeks, and then monthly
- if concentrations increase to more than 5 times the upper limit of normal bosentan should be stopped; reintroduction may be considered when concentrations return to below the pretreatment value
- if concentrations increase above 8 times the upper limit of normal or there are symptoms of hepatotoxicity or increases in total bilirubin levels greater than twice the upper limit of normal, treatment should be stopped and not reintroduced

Haemoglobin concentrations should be monitored every 3 months during therapy, more frequently at the start.

Bosentan should not be given to patients with hypotension. Although there is no evidence of rebound effects after stopping bosentan, it is recommended that therapy should be withdrawn gradually.

Bosentan and related endothelin receptor antagonists are teratogenic in *rats* and should not be used in pregnancy or in women of child-bearing potential who are not using a reliable method of contraception; hormonal contraceptives alone may not be adequate and additional measures may be required (see Interactions, below).

Interactions

Bosentan is metabolised by the cytochrome P450 isoenzymes CYP2C9 and CYP3A4 and is also an inducer of the same isoenzymes. It may also possibly induce CYP2C19. Interactions may therefore occur with other drugs that are either metabolised by, or inhibit, these isoenzymes. Use with ciclosporin is contra-indicated since plasma concentrations of bosentan are significantly increased (see below). There is an increased risk of hepatotoxicity if bosentan is given with glibenclamide and such use should be avoided; the hypoglycaemic effect of glibenclamide may also be reduced. Bosentan has reduced the plasma concentrations of some hormonal contraceptives and additional contraceptive measures are advised (see Endothelin Receptor Antagonists, p.2068).

Anticoagulants. For reports of bosentan decreasing the anticoagulant effect of *warfarin*, see Endothelin Receptor Antagonists, p.1430.

Ciclosporin. There appears to be a complex interaction between bosentan and ciclosporin. In a pharmacokinetic study[1] in healthy subjects given both drugs, doses of ciclosporin needed increasing to achieve target trough ciclosporin concentrations; it was calculated that plasma concentrations of ciclosporin would otherwise have been reduced by about half in the presence of bosentan. In addition, plasma concentrations of bosentan were almost doubled by ciclosporin. Licensed product information for bosentan states that plasma concentrations at steady state are 3 to 4 times higher in the presence of ciclosporin and contra-indicates the combination.

1. Binet I, *et al.* Renal hemodynamics and pharmacokinetics of bosentan with and without cyclosporine A. *Kidney Int* 2000; **57:** 224–31.

Pharmacokinetics

Bosentan is absorbed from the gastrointestinal tract with an absolute bioavailability of about 50%. Peak plasma concentrations occur about 3 to 5 hours after an oral dose. It is more than 98% bound to plasma proteins, mainly to albumin. Bosentan is metabolised in the liver by the cytochrome P450 isoenzymes CYP2C9 and CYP3A4 and is an inducer of these enzymes and possibly also of CYP2C19; after multiple dosing, plasma concentrations of bosentan decrease gradually to 50 to 65% of those seen after a single dose. Bosentan has three metabolites, one of which is active. Bosentan is excreted almost entirely as metabolites in the bile; less than 3% of an oral dose is excreted in the urine. The terminal elimination half-life is about 5 hours.

◊ References.

1. Weber C, *et al.* Multiple-dose pharmacokinetics, safety, and tolerability of bosentan, an endothelin receptor antagonist, in healthy male volunteers. *J Clin Pharmacol* 1999; **39:** 703–14.
2. van Giersbergen PLM, *et al.* Influence of mild liver impairment on the pharmacokinetics and metabolism of bosentan, a dual endothelin receptor antagonist. *J Clin Pharmacol* 2003; **43:** 15–22.

Uses and Administration

Bosentan is an endothelin receptor antagonist (p.1155) used in the management of pulmonary hypertension (below) and systemic sclerosis (see Scleroderma, below). It has also been investigated in heart failure and in hypertension.

In **pulmonary hypertension**, patients over 12 years of age may be given bosentan orally in an initial dose of 62.5 mg twice daily, increased after 4 weeks to a maintenance dose of 125 mg twice daily. In those with low body weight (below 40 kg) both the initial and maintenance doses are 62.5 mg twice daily. For the use of bosentan in children, see below.