Bezalex; Bezalip; Bifaren; Bionolip; Colser; Fazebit; Klestran†; Lesbest; Lipocin; Neptalip; Nivetril; Redalip; Solibay†; Zaf; ***Neth.:*** Bezalip; ***NZ:*** Bezalip; Fibalip; ***Philipp.:*** Bezastad; ***Pol.:*** Bezamidin; ***Port.:*** Bezalip; ***S.Afr.:*** Bezalip; ***Singapore:*** Bezalip; Zafibral; ***Spain:*** Difaterol; Eulitop; Reductero†; ***Swed.:*** Bezalip; ***Switz.:*** Cedur; ***Thai.:*** Bezalip; Bezamil; Polyzalip; Raset†; ***UAE:*** Lipitrol; ***UK:*** Bezagen; Bezalip; Bezalip Mono; Fibrazate; Zimbacol; ***Venez.:*** Bezalip; Detrex†.

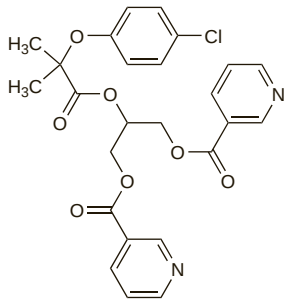
Binifibrate *(rINN)*

Binifibrato; Binifibratum. 2-(4-Chlorophenoxy)-2-methylpropionic acid ester with 1,3-dinicotinoyloxypropan-2-ol.

Бинифибрат

$C_{25}H_{23}ClN_2O_7$ = 498.9.

CAS — 69047-39-8.



Profile

Binifibrate, a derivative of clofibrate (p.1246) and nicotinic acid (p.1957), is a lipid regulating drug that has been used in the treatment of hyperlipidaemias.

Preparations

Proprietary Preparations (details are given in Part 3)
Spain: Antopal†; Biniwas†.

Bisoprolol Fumarate

(BANM, USAN, rINNM) ⊗

Bisoprolol Fumarat; Bisoprolol, Fumarate de; Bisoprolol Hemifumarate; Bisoprolol, hémifumarate de; Bisoprololfumarat; Bisoprololi Fumaras; Bisoprololi hemifumaras; Bisoprololifumaraatti; CL-297939; EMD-33512 (bisoprolol or bisoprolol fumarate); Fumarato de bisoprolol. 1-[4-(2-Isopropoxyethoxymethyl)phenoxy]-3-isopropylaminopropan-2-ol fumarate.

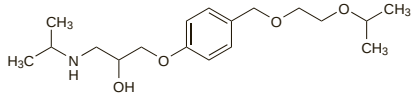
Бизопролола Фумарат

$(C_{18}H_{31}NO_4)_2,C_4H_4O_4$ = 767.0.

CAS — 66722-44-9 (bisoprolol); 66722-45-0 (bisoprolol fumarate); 104344-23-2 (bisoprolol fumarate).

ATC — C07AB07.

ATC Vet — QC07AB07.



(bisoprolol)

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Bisoprolol Fumarate). A white or almost white, slightly hygroscopic powder. It exhibits polymorphism. Very soluble in water; freely soluble in methyl alcohol. Store in airtight containers. Protect from light.

USP 31 (Bisoprolol Fumarate). A white crystalline powder. Very soluble in water and in methyl alcohol; freely soluble in alcohol, in chloroform, and in glacial acetic acid; slightly soluble in acetone and in ethyl acetate. Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p.1226.

Interactions

The interactions associated with beta blockers are discussed on p.1228.

Pharmacokinetics

Bisoprolol is almost completely absorbed from the gastrointestinal tract and undergoes only minimal first-pass metabolism resulting in an oral bioavailability of about 90%. Peak plasma concentrations are reached 2 to 4 hours after oral doses. Bisoprolol is about 30% bound to plasma proteins. It has a plasma elimination half-life of 10 to 12 hours. Bisoprolol is moderately lipid-soluble. It is metabolised in the liver and excreted in urine, about 50% as unchanged drug and 50% as metabolites.

Uses and Administration

Bisoprolol is a cardioselective beta blocker (p.1225). It is reported to be devoid of intrinsic sympathomimetic and membrane-stabilising properties.

Bisoprolol is given as the fumarate in the management of hypertension (p.1171) and angina pectoris (p.1157). It is also used as an adjunct to standard therapy in patients with stable chronic heart failure (p.1165).

In **hypertension** or **angina pectoris** the usual dose of bisoprolol fumarate is 5 to 10 mg orally as a single daily dose; the maximum recommended dose is 20 mg daily. A reduction in dose may be necessary in patients with hepatic or renal impairment (see below).

In **heart failure** the initial oral dose of bisoprolol fumarate is 1.25 mg once daily. If tolerated, the dose should be doubled after 1 week, and then increased gradually at 1 to 4 week intervals to the maximum dose tolerated; this should not exceed 10 mg once daily.

◊ References.

1. Johns TE, Lopez LM. Bisoprolol: is this just another beta-blocker for hypertension or angina? *Ann Pharmacother* 1995; **29:** 403–14.
2. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999; **353:** 9–13.
3. McGavin JK, Keating GM. Bisoprolol: a review of its use in chronic heart failure. *Drugs* 2002; **62:** 2677–96.

Administration in hepatic or renal impairment. US licensed product information recommends that the initial dose of bisoprolol fumarate for hypertension should be 2.5 mg daily and that the dose should be increased cautiously in patients with severe hepatic impairment or renal impairment (creatinine clearance less than 40 mL/minute). UK licensed product information recommends a maximum dose of 10 mg daily for both angina pectoris and hypertension in patients with severe hepatic impairment or with a creatinine clearance of less than 20 mL/minute.

Bisoprolol is not dialysable.

Preparations

USP 31: Bisoprolol Fumarate and Hydrochlorothiazide Tablets; Bisoprolol Fumarate Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Concor; Corbis; Lostaprolol; ***Austral.:*** Bicor; ***Austria:*** Bisocor; Bisostad; Bisotyrol†; Cardiocor; Concor; Darbalan; Nanalan; Rivacor; ***Belg.:*** Bisoprotop; Docbisopro; Emconcor; Isoten; ***Braz.:*** Concor; ***Canad.:*** Monocor; ***Chile:*** Concor; ***Cz.:*** Bisoblock; Bisocard; Bisogamma; Bivaxol; Concor; Concor Cor; Kordobis; Rivocor; ***Denm.:*** Bisocor; Cardicor; Emconcor; ***Fin.:*** Bisomerck; Bisopral; Emconcor; Orloc; ***Fr.:*** Cardensiel; Cardiocor; Detensiel; Soprol†; ***Ger.:*** Biso; Biso Lich; Biso-Puren; BisoAPS; Bisobeta; Bisobloc†; Bisogamma; Bisohexal; Bisomerck; Concor; Cordalin†; Fondril; Jutabis; ***Gr.:*** Abitrol; Blocatens; Pactens; Speridol; ***Hong Kong:*** Concor; ***Hung.:*** Bisoblock; Bisocard; Bisogamma; Bisogen; Concor; Concor Cor; Coviogal; ***India:*** Concor; ***Indon.:*** B-Beta; Concor; Hapsen; Lodoz; Maintate; ***Irl.:*** Bisocor; Bisopine; Cardicor; Emcolol; Emcor; Soprol; ***Israel:*** Bisolol; Cardiloc; Concor; ***Ital.:*** Cardicor; Concor; Congescor; Pluscor; Sequacor; ***Jpn:*** Maintate; ***Malaysia:*** Concor; ***Mex.:*** Concor; ***Neth.:*** Bisobloc†; Bisoblock; Cardicor†; Emcor; ***Norw.:*** Emconcor; ***Philipp.:*** Concore; ***Pol.:*** Bisocard; Bisohexal; Bisopromerck; Bisoratio; Concor; Corectin; ***Port.:*** Concor; Libracor; ***Rus.:*** Biprol (Бипрол); Bisocard (Бисокард); Bisogamma (Бисогамма); Concor (Конкор); Corbis (Корбис); ***S.Afr.:*** Adco-Bisocor; Bilocor; Bisohexal; Cardicor; Concor; ***Singapore:*** Concor; ***Spain:*** Emconcor; Euradal; Godal; ***Swed.:*** Bisomerck; Emconcor; ***Switz.:*** Bilol; Concor; ***Thai.:*** Concor; Novacor; ***Turk.:*** Concor; ***UK:*** Bipranix†; Cardicor; Emcor; Monocor†; Soloc†; Vivacor; ***USA:*** Zebeta; ***Venez.:*** Concor.

Multi-ingredient: ***Arg.:*** Corbis D; Ziac; ***Austria:*** Bisocombin; Bisoprolol comp; Bisoprolol-HCT; Bisostad plus; Concor Plus; Darbalan Plus; Nanalan Plus; Rivacor Plus; ***Belg.:*** Co-Bisoprolol; Emcoretic; Lodoz; Maxsoten; Merck-Co-Bisoprolol; ***Braz.:*** Biconcor; ***Chile:*** Ziac; ***Cz.:*** Concor Plus†; Lodoz; Tebis Plus H; ***Fin.:*** Bisoprolol Comp; Emconcor Comp; Orloc Comp; ***Fr.:*** Lodoz; Wytens; ***Ger.:*** Biso comp; Biso-Puren comp; Bisobeta comp; Bisohexal plus; BisoLich comp; Bisomerck Plus; Bisoplus; Bisoprolol Comp; Bisoprolol HCT; Bisoprolol Plus; Concor Plus; Fondril HCT; ***Hong Kong:*** Lodoz; ***Hung.:*** Concor Plus; Lodoz; ***India:*** Lodoz; ***Ital.:*** Lodoz; ***Mex.:*** Biconcor; ***Neth.:*** Emcoretic; ***Norw.:*** Lodoz; ***Philipp.:*** Ziac; ***Port.:*** Concor Plus; ***S.Afr.:*** Ziak; ***Singapore:*** Lodoz; ***Spain:*** Emcoretic; ***Switz.:*** Concor Plus; Lodoz; ***Thai.:*** Lodoz; ***USA:*** Ziac; ***Venez.:*** Biconcor; Ziac.

Bivalirudin *(BAN, USAN, rINN)*

BG-8967; Bivalirudina; Bivalirudine; Bivalirudinum; Hirulog.

Бивалирудин

$C_{98}H_{138}N_{24}O_{33}$ = 2180.3.

CAS — 128270-60-0.

ATC — B01AE06.

ATC Vet — QB01AE06.

Incompatibility. The manufacturer of bivalirudin states that it is incompatible with: alteplase, amiodarone hydrochloride, amphotericin B, chlorpromazine hydrochloride, diazepam, prochlorperazine edisilate, reteplase, streptokinase, and vancomycin hydrochloride.

Adverse Effects and Precautions

As for Lepirudin, p.1323.

Interactions

As for Lepirudin, p.1323.

Pharmacokinetics

Bivalirudin is partly metabolised and partly excreted by the kidney. When given intravenously the plasma half-life is about 25 minutes in patients with normal renal function but is prolonged in renal impairment. Bivalirudin does not bind to plasma proteins and is removed by haemodialysis.

◊ References.

1. Robson R, *et al.* Bivalirudin pharmacokinetics and pharmacodynamics: effect of renal function, dose, and gender. *Clin Pharmacol Ther* 2002; **71:** 433–9.

Uses and Administration

Bivalirudin, an analogue of the peptide hirudin (p.1305), is a direct thrombin inhibitor with actions similar to Lepirudin, p.1323. It is used as an anticoagulant in patients undergoing percutaneous coronary interventions, including those with, or at risk of, heparin-induced thrombocytopenia. It is also used in patients with acute coronary syndromes in whom early intervention is planned, and has been investigated in patients with acute coronary syndromes treated medically (see Ischaemic Heart Disease, under Uses and Administration of Lepirudin, p.1323).

Some preparations state that bivalirudin is present as the hydrate of the trifluoroacetate salt but doses are given in terms of bivalirudin.

In the management of patients undergoing **planned percutaneous coronary intervention** (PCI), the initial dose of bivalirudin is 750 micrograms/kg by intravenous injection followed immediately by an intravenous infusion of 1.75 mg/kg per hour; the activated clotting time should be measured 5 minutes after the initial injection and a second injection of 300 micrograms/kg should be given if anticoagulation is inadequate. The infusion should be given for the duration of the procedure and may be continued for up to 4 hours afterwards; licensed prescribing information in the USA allows the infusion to then be continued at a lower dose of 200 micrograms/kg per hour for up to 20 hours if required.

As part of the management of patients with **acute coronary syndromes**, the initial dose of bivalirudin is 100 micrograms/kg by intravenous injection, followed by an intravenous infusion of 250 micrograms/kg per hour. In patients managed *medically*, the infusion may be continued for up to 72 hours. For those who proceed to *PCI or coronary artery bypass surgery without cardiopulmonary bypass*, a further intravenous injection of 500 micrograms/kg should be given, and the infusion should be increased to 1.75 mg/kg per hour for the duration of the procedure; after PCI, the infusion may be continued at a dose of 250 micrograms/kg per hour for a further 4 to 12 hours if required. For those who proceed to *coronary artery bypass surgery with cardiopulmonary bypass*, the infusion should be stopped 1 hour before the procedure and the patient should be treated with unfractionated heparin.

The dose of bivalirudin should be reduced in patients with renal impairment (see below).

◊ References.

1. Carswell CI, Plosker GL. Bivalirudin: a review of its potential place in the management of acute coronary syndromes. *Drugs* 2002; **62:** 841–70.
2. Sciulli TM, Mauro VF. Pharmacology and clinical use of bivalirudin. *Ann Pharmacother* 2002; **36:** 1028–41.
3. Moen MD, *et al.* Bivalirudin: a review of its use in patients undergoing percutaneous coronary intervention. *Drugs* 2005; **65:** 1869–91.

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.

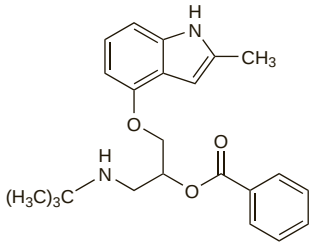
Бопиндолола Малонат

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

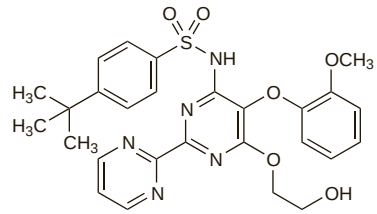
Бозентан

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