Bezafibrate *(BAN, USAN, rINN)*

Betsafibraatti; Bezafibrát; Bezafibrat; Bezafibratas; Bézafibrate; Bezafibrato; Bezafibratum; BM-15075; LO-44. 2-[4-(2-*p*-Chlorobenzamidoethyl)phenoxy]-2-methylpropionic acid.

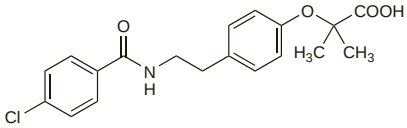
Безафибрат

$C_{19}H_{20}ClNO_4$ = 361.8.

CAS — 41859-67-0.

ATC — C10AB02.

ATC Vet — QC10AB02.



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

Ph. Eur. 6.2 (Bezafibrate). A white or almost white, crystalline powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in alcohol and in acetone; freely soluble in dimethylformamide; it dissolves in dilute solutions of alkali hydroxides.

Adverse Effects and Precautions

The commonest adverse effects of bezafibrate therapy are gastrointestinal disturbances including anorexia, nausea, and gastric discomfort. Other adverse effects reported to occur less frequently include headache, dizziness, vertigo, fatigue, skin rashes, pruritus, photosensitivity, alopecia, impotence, anaemia, leucopenia, and thrombocytopenia. Raised serum-aminotransferase concentrations have occasionally been reported. Elevated creatine phosphokinase concentrations during bezafibrate therapy may be associated with a syndrome of myositis, myopathy, and rarely rhabdomyolysis; patients with hypoalbuminaemia resulting from nephrotic syndrome or with renal impairment may be at increased risk. Bezafibrate should not be given with statins in patients with risk factors for myopathy. Bezafibrate may increase the lithogenic index, and there have been isolated reports of gallstones, although the risk from fibrates as a class is unclear (see Gallstones, below).

Bezafibrate should not be given to patients with severe hepatic impairment or significant liver disease, gallstones or gallbladder disorders, or hypoalbuminaemic states such as nephrotic syndrome. It should be used with caution in renal impairment and is contra-indicated if creatinine clearance is below 15 mL/minute unless the patient is on dialysis (see under Uses and Administration, below).

◊ Reviews.

1. Davidson MH, *et al.* Safety considerations with fibrate therapy. *Am J Cardiol* 2007; **99** (Issue 6 suppl 1): 3C–18C.

Effects on glucose metabolism. Use of fibrates in diabetic patients has generally been reported to either improve[1-3] or have no effect[4-6] on insulin sensitivity and glucose metabolism, and they are considered a suitable treatment for type 2 diabetics with hypertriglyceridaemia.[7] There is also some evidence that fibrates may reduce the incidence or delay the onset of diabetes in patients with obesity[8] or impaired glucose tolerance.[9] However, there has been a report[10] of recurrent hypoglycaemia in a type 2 diabetic when gemfibrozil was added to high-dose insulin therapy although eventually a reduced insulin dosage, with fibrate therapy, produced good glucose control. Gemfibrozil is contraindicated in patients receiving repaglinide due to the risk of severe hypoglycaemia (see p.458). Conversely, a study in 20 diabetic patients[11] given gemfibrozil reported a slight increase in requirements for antidiabetic therapy (oral hypoglycaemics or insulin) in 9 and a decrease in 1.

1. Ogawa S, *et al.* Bezafibrate reduces blood glucose in type 2 diabetes mellitus. *Metabolism* 2000; **49:** 331–4.
2. Jones IR, *et al.* Lowering of plasma glucose concentrations with bezafibrate in patients with moderately controlled NIDDM. *Diabetes Care* 1990; **13:** 855–63.
3. Notarbartolo A, *et al.* Effects of gemfibrozil in hyperlipidemic patients with or without diabetes. *Curr Ther Res* 1993; **53:** 381–93.
4. Leaf DA, *et al.* The hypolipidemic effects of gemfibrozil in type V hyperlipidemia. *JAMA* 1989; **262:** 3154–60.
5. Pagani A, *et al.* Effect of short-term gemfibrozil administration on glucose metabolism and insulin secretion in non-insulin-dependent diabetics. *Curr Ther Res* 1989; **45:** 14–20.
6. Hernández-Mijares A, *et al.* Ciprofibrate effects on carbohydrate and lipid metabolism in type 2 diabetes mellitus subjects. *Nutr Metab Cardiovasc Dis* 2000; **10:** 1–6.
7. Buse JB, *et al.* Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. *Circulation* 2007; **115:** 114–26. Also published in *Diabetes Care* 2007; **30:** 162–72.
8. Tenenbaum A, *et al.* Effect of bezafibrate on incidence of type 2 diabetes mellitus in obese patients. *Eur Heart J* 2005; **26:** 2032–8.
9. Tenenbaum A, *et al.* Peroxisome proliferator-activated receptor ligand bezafibrate for prevention of type 2 diabetes mellitus in patients with coronary artery disease. *Circulation* 2004; **109:** 2197–2202.
10. Klein J, *et al.* Recurrent hypoglycaemic episodes in a patient with type 2 diabetes under fibrate therapy. *J Diabetes Complications* 2002; **16:** 246–8.
11. Konttinen A, *et al.* The effect of gemfibrozil on serum lipids in diabetic patients. *Ann Clin Res* 1979; **11:** 240–5.

Effects on the kidneys. Small increases in creatinine concentration are common during treatment with bezafibrate and have also been reported with other fibrates,[1] although possibly not with gemfibrozil. There have also been reports of acute renal failure associated with treatment with bezafibrate,[2] and with clofibrate,[3,4] and an accelerated decline in renal function has been reported with bezafibrate in patients with chronic renal failure.[5] Renal failure may also occur due to rhabdomyolysis in patients receiving fibrates, including gemfibrozil (see Effects on Skeletal Muscle, below).

1. Broeders N, *et al.* Fibrate-induced increase in blood urea and creatinine: is gemfibrozil the only innocuous agent? *Nephrol Dial Transplant* 2000; **15:** 1993–9.
2. Lipkin GW, Tomson CRV. Severe reversible renal failure with bezafibrate. *Lancet* 1993; **341:** 371.
3. Dosa S, *et al.* Acute-on-chronic renal failure precipitated by clofibrate. *Lancet* 1976; **i:** 250.
4. Cumming A. Acute renal failure and interstitial nephritis after clofibrate treatment. *BMJ* 1980; **281:** 1529–30.
5. Williams AJ, *et al.* The short term effects of bezafibrate on the hypertriglyceridaemia of moderate to severe uraemia. *Br J Clin Pharmacol* 1984; **18:** 361–7.

Effects on the nervous system. Adverse effects on the peripheral nervous system have been reported with fibrates. Peripheral neuropathy has been reported[1] with bezafibrate, and was substantiated by nerve conduction studies. There have also been reports of peripheral neuropathy with clofibrate,[2] and with fenofibrate,[3] which resolved when therapy was withdrawn. In addition, by 1993, the Adverse Drug Reactions Advisory Committee in Australia had received reports of paraesthesia occurring in 6 patients in association with gemfibrozil treatment.[4]

1. Ellis CJ, *et al.* Peripheral neuropathy with bezafibrate. *BMJ* 1994; **309:** 929.
2. Gabriel R, Pearce JMS. Clofibrate-induced myopathy and neuropathy. *Lancet* 1976; **ii:** 906.
3. Corcia P, *et al.* Severe toxic neuropathy due to fibrates. *J Neurol Neurosurg Psychiatry* 1999; **66:** 410.
4. Anonymous. Paraesthesia and neuropathy with hypolipidaemic agents. *Aust Adverse Drug React Bull* 1993; **12:** 6.

Effects on the pancreas. Acute pancreatitis has been reported[1] in a patient receiving bezafibrate, and recurred on 2 occasions when bezafibrate was restarted. There has also been a report[2] of acute pancreatitis in a patient receiving both fenofibrate and simvastatin, although simvastatin was considered more likely to be responsible. An increased incidence of pancreatitis was also reported with fenofibrate in the FIELD study,[3] although the number of cases was small.

1. Gang N, *et al.* Relapsing acute pancreatitis induced by re-exposure to the cholesterol lowering agent bezafibrate. *Am J Gastroenterol* 1999; **94:** 3626–8.
2. McDonald KB, *et al.* Pancreatitis associated with simvastatin plus fenofibrate. *Ann Pharmacother* 2002; **36:** 275–9.
3. The FIELD study investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet* 2005; **366:** 1849–61. Corrections. *ibid.* 2006; **368:** 1415 and 1420.

Effects on sexual function. Sexual dysfunction has occurred with some fibrates. *Erectile dysfunction* and *loss of libido* has been reported in 3 patients[1-3] during gemfibrozil treatment. In 2 of the men[1,2] bezafibrate did not produce this adverse effect. The UK CSM was reported to be aware of a further 6 cases.[2] Of a further 3 cases of erectile dysfunction associated with gemfibrozil reported from Spain, 1 patient had previously reacted similarly to clofibrate.[4] A systematic review,[5] including these and other reports, supported the conclusion that fibrates could cause erectile dysfunction.

Gynaecomastia was reported[6] in a 56-year-old man receiving fenofibrate and recurred on rechallenge; there were no other effects on sexual function.

1. Pizarro S, *et al.* Gemfibrozil-induced impotence. *Lancet* 1990; **336:** 1135.
2. Bain SC, *et al.* Gemfibrozil-induced impotence. *Lancet* 1990; **336:** 1389.
3. Bharani A. Sexual dysfunction after gemfibrozil *BMJ* 1992; **305:** 693.
4. Figueras A, *et al.* Gemfibrozil-induced impotence. *Ann Pharmacother* 1993; **27:** 982.
5. Rizvi K, *et al.* Do lipid-lowering drugs cause erectile dysfunction? A systematic review. *Fam Pract* 2002; **19:** 95–8.
6. Gardette V, *et al.* Gynecomastia associated with fenofibrate. *Ann Pharmacother* 2007; **41:** 508–11.

Effects on skeletal muscle. Muscle disorders including myositis and myopathy are well known to occur with lipid regulating drugs such as fibrates.[1] Rhabdomyolysis, presenting as muscle pain with elevated creatine phosphokinase and myoglobinuria leading to renal failure, has also been reported but appears to be rare. Patients with renal impairment, and possibly with hypothyroidism, may be at increased risk of muscle toxicity. The UK CSM has advised[1] that patients treated with fibrates should consult their doctor if they develop muscle pain, tenderness, or weakness, and treatment should be stopped if muscle toxicity is suspected clinically or if creatine phosphokinase is markedly raised or progressively rising.

Other lipid regulating drugs, particularly the statins, have also been associated with myopathy and the risk of muscle toxicity is increased if fibrates and statins are taken together (see Lipid Regulating Drugs under Interactions of Simvastatin, p.1393); combination therapy may be appropriate in some patients but careful monitoring is required.[2]

1. Committee on Safety of Medicines/Medicines Control Agency. Rhabdomyolysis associated with lipid-lowering drugs. *Current Problems* 1995; **21:** 3. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015618&RevisionSelectionMethod=LatestReleased (accessed 30/05/08)
2. Shek A, Ferrill MJ. Statin-fibrate combination therapy. *Ann Pharmacother* 2001; **35:** 908–917.

Gallstones. Fibrates, including fenofibrate[1-3] and gemfibrozil[4] have been reported to increase indices of bile lithogenicity, and some studies[5,6] have suggested an increased risk of gallstones in patients receiving fibrates. However, in the Helsinki Heart Study[7] no significant increase in gallstone operations was reported among 2051 patients taking gemfibrozil compared with 2030 taking placebo, although a follow-up study[8] reported that cholecystectomies were consistently more common in those receiving gemfibrozil during the entire 8.5-year observation period.

1. Brown WV. Treatment of hypercholesterolaemia with fenofibrate: a review. *Curr Med Res Opin* 1989; **11:** 321–30.
2. Blane GF. Comparative toxicity and safety profile of fenofibrate and other fibric acid derivatives. *Am J Med* 1987; **83** (suppl 5B): 26–36.
3. Palmer RH. Effects of fibric acid derivatives on biliary lipid composition. *Am J Med* 1987; **83** (suppl 5B): 37–43.
4. Leiss O, *et al.* Effect of gemfibrozil on biliary lipid metabolism in normolipemic subjects. *Metabolism* 1985; **34:** 74–82.
5. Mamdani MM, *et al.* Is there an association between lipid-lowering drugs and cholecystectomy? *Am J Med* 2000; **108:** 418–21.
6. Caroli-Bosc F-X, *et al.* Role of fibrates and HMG-CoA reductase inhibitors in gallstone formation: epidemiological study in an unselected population. *Dig Dis Sci* 2001; **46:** 540–4.
7. Frick MH, *et al.* Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia: safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med* 1987; **317:** 1237–45.
8. Huttunen JK, *et al.* The Helsinki Heart Study: an 8.5-year safety and mortality follow-up. *J Intern Med* 1994; **235:** 31–9.

Headache. Severe recurrent headaches have been reported[1] in a patient receiving bezafibrate. The headaches started about 24 hours after therapy with bezafibrate began, and recurred about 1 hour after each dose. Headaches occurred 30 to 90 minutes after each dose of gemfibrozil in 2 patients.[2,3] In both patients, the headaches were accompanied by dry mouth, and in 1 also by blurred vision. The headaches stopped when gemfibrozil was withdrawn and recurred one week after re-exposure.

1. Hodgetts TJ, Tunnicliffe C. Bezafibrate-induced headache. *Lancet* 1989; **i:** 163.
2. Arellano F, *et al.* Gemfibrozil-induced headache. *Lancet* 1988; **i:** 705.
3. Alvarez-Sabin J, *et al.* Gemfibrozil-induced headache. *Lancet* 1988; **ii:** 1246.

Hyperhomocysteinaemia. Hyperhomocysteinaemia has been associated with an increased risk for cardiovascular disease. Small studies have found that both bezafibrate[1,2] and fenofibrate[1,3] increase plasma-homocysteine concentrations, although the clinical significance of this is not clear.[4] Folic acid and vitamin B_{12} have been given[4,5] with fenofibrate to reduce homocysteine concentrations, but the role of such treatment is not established.

1. Dierkes J, *et al.* Serum homocysteine increases after therapy with fenofibrate or bezafibrate. *Lancet* 1999; **354:** 219–20.
2. Jonkers IJAM, *et al.* Implication of fibrate therapy for homocysteine. *Lancet* 1999; **354:** 1208.
3. de Lorgeril M, *et al.* Lipid-lowering drugs and homocysteine. *Lancet* 1999; **353:** 209–10.
4. Dierkes J, *et al.* Fenofibrate-induced hyperhomocysteinaemia: clinical implications and management. *Drug Safety* 2003; **26:** 81–91.
5. Melenovsky V, *et al.* Effect of folic acid on fenofibrate-induced elevation of homocysteine and cysteine. *Am Heart J* 2003; **146:** 110. Full version available at: http://download.journals.elsevierhealth.com/pdfs/journals/0002-8703/PIIS0002870303001224.pdf (accessed 30/05/08)

Photosensitivity. Fibrates have been associated with photosensitivity reactions[1] and there may be cross-sensitivity with ketoprofen (see under Adverse Effects of Ketoprofen, p.73).

1. Serrano G, *et al.* Photosensitivity induced by fibric acid derivatives and its relation to photocontact dermatitis to ketoprofen *J Am Acad Dermatol* 1992; **27:** 204–8.

Interactions

Bezafibrate and other fibrates are highly protein-bound and may displace other drugs from protein binding sites. Interactions may also occur through changes in the activity of cytochrome P450 isoenzymes, particularly CYP3A4.

Fibrates may enhance the effects of oral anticoagulants; the dose of anticoagulant should be reduced when treatment with a fibrate is started, and then adjusted gradually if necessary. Recommendations vary; licensed product information for bezafibrate suggests a reduction of up to 50% in the dosage of anticoagulant. The mechanism of the interaction is unclear; fibrates have been reported to displace warfarin from protein binding sites but other mechanisms are probably also involved.

Other drugs that may be displaced from plasma proteins by fibrates include tolbutamide and other sulfonylurea antidiabetics, phenytoin, and, in patients with hypoalbuminaemia, furosemide. The interaction with antidiabetics is complex since fibrates may alter glucose tolerance in diabetic patients (see Effects on Glucose Metabolism, above). The dosage of antidiabetics may need adjusting during bezafibrate therapy.

There is an increased risk of myopathy if fibrates are used with statins (see Lipid Regulating Drugs under Interactions of Simvastatin, p.1393).

Fibrates may interact with ciclosporin, although reports have been conflicting (see p.1827). However, nephrotoxicity associated with increased ciclosporin concentrations has been reported with bezafibrate and renal function should be monitored.

Cholestasis has been reported in a patient given fenofibrate with raloxifene (see p.2128).

◊ Reviews.

1. Lozada A, Dujovne CA. Drug interactions with fibric acids. *Pharmacol Ther* 1994; **63:** 163–76.

Lipid regulating drugs. The bioavailability of gemfibrozil was reduced by *colestipol*, but was unaffected when gemfibrozil was taken either 2 hours before or 2 hours after colestipol.[1]

For discussion of the interaction between fibrates and *statins*, see p.1393.

1. Forland SC, *et al.* Apparent reduced absorption of gemfibrozil when given with colestipol. *J Clin Pharmacol* 1990; **30:** 29–32.

NSAIDs. Acute renal failure due to rhabdomyolysis in a patient has been attributed to an interaction between ciprofibrate and *ibuprofen*.[1] Ibuprofen was believed to have displaced ciprofibrate from protein binding sites. The use of radiological contrast media may also have been a contributory factor.

1. Ramachandran S, *et al.* Acute renal failure due to rhabdomyolysis in presence of concurrent ciprofibrate and ibuprofen treatment. *BMJ* 1997; **314:** 1593.

Pharmacokinetics

Bezafibrate is readily absorbed from the gastrointestinal tract. Plasma protein binding is about 95%. The plasma elimination half-life is about 1 to 2 hours. Most of a dose is excreted in the urine, about half as unchanged drug, the remainder as metabolites including 20% as glucuronides. A small proportion (about 3%) of the dose appears in the faeces. Elimination may be increased by forced diuresis. The drug is not dialysable.

◊ References.

1. Abshagen U, *et al.* Disposition pharmacokinetics of bezafibrate in man. *Eur J Clin Pharmacol* 1979; **16:** 31–8.
2. Abshagen U, *et al.* Steady-state kinetics of bezafibrate and clofibrate in healthy female volunteers. *Eur J Clin Pharmacol* 1980; **17:** 305–8.

The elderly. In a study comparing the pharmacokinetics of bezafibrate in 19 elderly patients with younger healthy subjects,[1] maximum plasma concentrations were 1.6 times higher in the elderly group (median 12.1 mg/litre against 7.7 mg/litre) and half-life was increased by 3.8 times (median 6.6 hours against 1.7 hours). The differences could not be attributed solely to diminished renal function in elderly patients. Dosage adjustments in elderly patients should not therefore be based on renal function alone.

1. Neugebauer G, *et al.* Steady-state kinetics of bezafibrate retard in hyperlipidemic geriatric patients. *Klin Wochenschr* 1988; **66:** 250–6.

Renal impairment. The half-life of bezafibrate may be prolonged in patients with renal impairment (see under Uses and Administration, below).

Uses and Administration

Bezafibrate, a fibric acid derivative, is a lipid regulating drug. It is used to reduce total cholesterol and triglycerides in the management of hyperlipidaemias (p.1169), including type IIa, type IIb, type III, type IV, and type V hyperlipoproteinaemias. Bezafibrate and other fibrates reduce triglycerides by reducing the concentration of very-low-density lipoprotein (VLDL). They reduce low-density lipoprotein (LDL)-cholesterol to a lesser extent, although the effect is variable, and may also increase high-density lipoprotein (HDL)-cholesterol. Although evidence that this leads to a reduction in cardiovascular events is less good than for statins, some fibrates may have a role in cardiovascular risk reduction (see below).

Bezafibrate is given in a usual oral dose of 200 mg three times daily taken with or after food; gastrointestinal disturbances may be reduced in susceptible patients by increasing the dose gradually over 5 to 7 days; 200 mg twice daily may occasionally be adequate for maintenance particularly in the treatment of hypertriglyceridaemia. A modified-release tablet is also available and is given as a single daily dose of 400 mg.

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

◊ General reviews.

1. Goa KL, *et al.* Bezafibrate: an update of its pharmacology and use in the management of dyslipidaemia. *Drugs* 1996; **52:** 725–53.
2. Goldenberg I, *et al.* Update on the use of fibrates: focus on bezafibrate. *Vasc Health Risk Manag* 2008; **4:** 131–41.

Action. Bezafibrate is a typical member of the fibric acid derivative group of drugs (the fibrates) used in the treatment of hyperlipidaemias (p.1169). One of the primary actions of the fibrates is to promote the catabolism of triglyceride-rich lipoproteins, in particular very-low-density lipoproteins (VLDL), apparently mediated by an enhanced activity of lipoprotein lipase.[1] They may also interfere with the synthesis of VLDL, possibly by inhibiting hepatic acetyl coenzyme A carboxylase. The effect of fibrates on low-density lipoprotein (LDL)-cholesterol depends on the overall lipoprotein status of the patient but concentrations tend to decrease if high at baseline and increase if low at baseline. High-density lipoprotein (HDL)-cholesterol concentrations are increased, although there have been a few reports of unexpected falls in HDL-cholesterol with bezafibrate[2,3] and ciprofibrate.[4,5]

Fibrates have three actions on sterol metabolism:[1] they inhibit the synthesis of cholesterol, they inhibit the synthesis of bile acids, and they enhance the secretion of cholesterol in bile. It is these latter two effects which are responsible for the raised cholesterol saturation of bile, which may lead to the formation of gallstones in some patients (see Gallstones, under Adverse Effects, above).

The effects of fibrates are mediated by their agonist action at peroxisome proliferator-activated receptors (PPARs).[6,7] Fibrates are agonists of PPAR-α, which plays an important role in fatty acid metabolism; some, such as bezafibrate, may also activate other receptors including PPAR-γ (which plays a role in glucose homoeostasis).[7]

1. Grundy SM, Vega GL. Fibric acids: effects on lipids and lipoprotein metabolism. *Am J Med* 1987; **83** (suppl 5B): 9–20.
2. Capps NE. Lipid profiles on fibric-acid derivatives. *Lancet* 1994; **344:** 684–5.
3. McLeod AJ, *et al.* Abnormal lipid profiles on fibrate derivatives. *Lancet* 1996; **347:** 261.
4. Chandler HA, Batchelor AJ. Ciprofibrate and lipid profile. *Lancet* 1994; **344:** 128–9.
5. McLeod AJ, *et al.* Ciprofibrate and lipid profile. *Lancet* 1994; **344:** 955.
6. Fruchart J-C, Duriez P. Mode of action of fibrates in the regulation of triglyceride and HDL-cholesterol metabolism. *Drugs Today* 2006; **42:** 39–64.
7. Robinson JG. Should we use PPAR agonists to reduce cardiovascular risk? *PPAR Res* 2008; **2008:** 891425.

Administration in renal impairment. Bezafibrate is mainly excreted in the urine and dosage alterations may be necessary in patients with renal impairment; fibrates may also impair renal function (see Effects on the Kidneys under Adverse Effects, above). Modified-release preparations are contra-indicated in patients with creatinine clearance (CC) below 60 mL/minute and the dosage of conventional-release formulations should be reduced depending on CC, as follows:

- CC 40 to 60 mL/minute: 400 mg daily
- CC 15 to 40 mL/minute: 200 mg daily or on alternate days
- CC less than 15 mL/minute unless on dialysis: contra-indicated
- dialysis patients: 200 mg every 3 days, with careful monitoring

In a study in patients with renal impairment[1] the half-life of bezafibrate was reported to be prolonged to 4.6 hours in 3 patients with CC greater than 40 mL/minute, 7.8 hours in 8 patients with CC of 20 to 40 mL/minute, and 20.1 hours in a patient with CC of 13 mL/minute.

1. Anderson P, Norbeck H-E. Clinical pharmacokinetics of bezafibrate in patients with impaired renal function. *Eur J Clin Pharmacol* 1981; **21:** 209–14.

Cardiovascular risk reduction. Lipid lowering therapy has an important role in patients at risk of cardiovascular disease (p.1164). Although the evidence is less good than for statins, several studies have shown that fibrates may reduce both the progression of atherosclerosis and the incidence of cardiovascular events.[1]

In the Bezafibrate Coronary Atherosclerosis Intervention Trial (BECAIT)[2,3] treatment with bezafibrate for 5 years in young men (less than 45 years of age) after myocardial infarction resulted in fewer coronary events and slowed the progression of focal coronary atherosclerosis when compared with placebo. However, in older men with peripheral vascular disease,[4] bezafibrate had no effect on the incidence of coronary events and stroke together, although the severity of intermittent claudication was reduced and, in men under 65 years, there were fewer non-fatal coronary events. In the Diabetes Atherosclerosis Intervention Study (DAIS),[5] fenofibrate reduced the angiographic progression of coronary atherosclerosis in type 2 diabetics, and there were also fewer clinical events in those receiving fenofibrate; further analysis showed[6] reduced progression to microalbuminuria in the fenofibrate group. However, another study in type 2 diabetics, the FIELD study,[7] found no reduction in the risk of major coronary events with fenofibrate, although there were fewer non-fatal myocardial infarctions and revascularisations. A meta-analysis[8] of studies including type 2 diabetics concluded that fibrates reduce the incidence of cardiovascular events, but the effect on mortality was not significant.

The best evidence for a reduction in cardiovascular events is for gemfibrozil. The Helsinki Heart Study[9] assessed gemfibrozil for the primary prevention of ischaemic heart disease in 4081 middle-aged men with hyperlipidaemia. There was an overall reduction of 34% in the incidence of fatal and non-fatal myocardial infarctions and cardiac deaths in the gemfibrozil group compared with the placebo group, with the greatest reduction seen during years 3 to 5. Follow-up for a further 3.5 years[10] suggested that long-term treatment with gemfibrozil seemed to postpone coronary events for about 5 years. The Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT)[11] assessed gemfibrozil for the secondary prevention of ischaemic heart disease in 2531 older men (mean age 64 years) whose primary lipid abnormality was a low HDL-cholesterol level. There was an overall reduction of 22% in the incidence of fatal and non-fatal myocardial infarctions and cardiac deaths in the gemfibrozil group compared with the placebo group, with the beneficial effects of gemfibrozil becoming apparent about 2 years after randomisation. There was also a reduction in the incidence of stroke.[12]

1. Després J-P, *et al.* Role of fibric acid derivatives in the management of risk factors for coronary heart disease. *Drugs* 2004; **64:** 2177–98.
2. Ericsson C-G, *et al.* Angiographic assessment of effects of bezafibrate on progression of coronary artery disease in young male postinfarction patients. *Lancet* 1996; **347:** 849–53.
3. Ericsson C-G, *et al.* Effect of bezafibrate treatment over five years on coronary plaques causing 20% to 50% diameter narrowing (The Bezafibrate Coronary Atherosclerosis Intervention Trial (BECAIT)). *Am J Cardiol* 1997; **80:** 1125–9.
4. Meade T, *et al.* Bezafibrate in men with lower extremity arterial disease: randomised controlled trial. *BMJ* 2002; **325:** 1139–43.
5. Diabetes Atherosclerosis Intervention Study Investigators. Effect of fenofibrate on progression of coronary-artery disease in type 2 diabetes: the Diabetes Atherosclerosis Intervention Study, a randomised study. *Lancet* 2001; **357:** 905–910. Correction. *ibid.*; 1890.
6. Ansquer J-C, *et al.* Fenofibrate reduces progression to microalbuminuria over 3 years in a placebo-controlled study in type 2 diabetes: results from the Diabetes Atherosclerosis Intervention Study (DAIS). *Am J Kidney Dis* 2005; **45:** 485–93.
7. The FIELD study investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet* 2005; **366:** 1849–61. Corrections. *ibid.* 2006; **368:** 1415 and 1420.
8. Allemann S, *et al.* Fibrates in the prevention of cardiovascular disease in patients with type 2 diabetes mellitus: meta-analysis of randomised controlled trials. *Curr Med Res Opin* 2006; **22:** 617–23.
9. Frick MH, *et al.* Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia: safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med* 1987; **317:** 1237–45.
10. Heinonen OP, *et al.* The Helsinki Heart Study: coronary heart disease incidence during an extended follow-up. *J Intern Med* 1994; **235:** 41–9.
11. Bloomfield Rubins H, *et al.* Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. *N Engl J Med* 1999; **341:** 410–18.
12. Bloomfield Rubins H, *et al.* Reduction in stroke with gemfibrozil in men with coronary heart disease and low HDL cholesterol: The Veterans Affairs HDL Intervention Trial (VA-HIT). *Circulation* 2001; **103:** 2828–33.

Dementia. For reference to a possible reduction in the incidence of dementia associated with lipid regulating drugs, including fibrates, see under Uses of Simvastatin, p.1395.

Preparations

BP 2008: Bezafibrate Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Bezacur; Bezalip; Elpi Lip; Nebufur; ***Austria:*** Bezacur; Bezalip; Bezaretard; Bezastad; ***Belg.:*** Cedur; Eulitop; ***Braz.:*** Cedur; ***Canad.:*** Bezalip; ***Chile:*** Nimus; Oralipin; ***Cz.:*** Regadrin B; ***Fin.:*** Bezalip; ***Fr.:*** Befizal; ***Ger.:*** Azufibrat†; Befibrat; Beza; Beza-Puren†; Bezabeta; Bezacur†; Bezadoc; Bezagamma; Bezamerck†; Bezapham†; Cedur; Lipox; Regadrin B†; Sklerofibrat†; ***Gr.:*** Bezalip; Getup†; Verbital; ***Hong Kong:*** Bezalip; Zafibral†; ***Hung.:*** Bezalip; ***India:*** Beza†; Bezalip; ***Israel:*** Bezalip; Norlip; ***Ital.:*** Bezalip; Hadiel; ***Jpn:*** Bezalip; ***Malaysia:*** Bezalip; ***Mex.:*** Befitec; Bexalcor; Bezafisal;

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†.

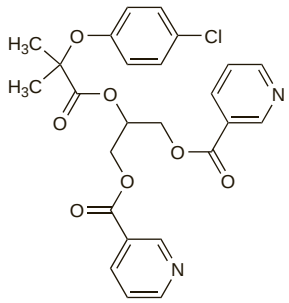
Binifibrate *(rINN)*

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.

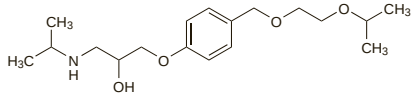
Бизопролола Фумарат

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