Tetanus. Autonomic overactivity, usually due to excessive catecholamine release, may occur as a complication of tetanus and is usually controlled with sedation (see p.1901). Beta blockers have also been used but may produce severe hypertension and are therefore not usually recommended. Labetalol has both alpha- and beta-blocking properties and intravenous labetalol has been used successfully to control the cardiovascular effects of tetanus,[1] although it has not been shown to offer any advantage over propranolol in this situation. Esmolol, a short-acting beta blocker, has also been used.[2]

1. Domenighetti GM, *et al.* Hyperadrenergic syndrome in severe tetanus: extreme rise in catecholamines responsive to labetalol. *BMJ* 1984; **288:** 1483–4.
2. King WW, Cave DR. Use of esmolol to control autonomic instability of tetanus. *Am J Med* 1991; **91:** 425–8.

Tetralogy of Fallot. For the use of beta blockers in the management of tetralogy of Fallot, see under Uses of Propranolol, p.1381.

Tremor. Tremor is a rhythmical oscillation of part of the body caused by involuntary contraction of opposing muscles. It may occur during action, maintenance of posture, or at rest, and varies in frequency and amplitude. Resting tremor is associated mainly with parkinsonism (p.791), whereas action tremor, which includes postural tremor and kinetic tremor, occurs in a wide variety of disorders. Treatment of the underlying disorder may remove the tremor. Drugs such as bronchodilators, tricyclic antidepressants, lithium, and caffeine may induce tremor; withdrawal of the causative drug usually alleviates the tremor. However, tremor often has no known underlying cause. Such tremor is referred to as **essential tremor** or benign essential tremor; it is usually postural and tends to affect the hands, head, voice, and sometimes the legs and trunk. It is exacerbated by emotional stress and anxiety. Essential tremor may appear at any age and is a lifelong condition that may progress with increasing age. In many cases there is a family history of the disorder (familial essential tremor).

Mild cases of essential tremor may not require regular drug treatment. Single doses of a beta blocker or a benzodiazepine may be useful in acute circumstances to control exacerbations provoked by stress. A single dose of propranolol usually produces a maximum effect after 1 to 2 hours and the effect may persist for several hours. Small amounts of alcohol may also provide effective temporary relief of essential tremor, although its regular use is obviously discouraged.

For more severe cases of essential tremor long-term drug treatment may be required (and may also be tried in other forms of tremor).[1-5] A beta blocker (usually a non-cardioselective beta blocker such as propranolol) is often the first drug used. Up to 70% of people have been reported to respond, although the average tremor reduction is only about 50 to 60%. The beneficial effect appears to be mainly due to blockade of peripheral $beta_2$ receptors on extrafusal muscle fibres and muscle spindles, although there may also be a CNS effect. Adverse effects may be troublesome on long-term use. Primidone may also be tried[6] although there may be a high incidence of acute adverse reactions after initial doses. Concern has been expressed that patients may become tolerant to these drugs given long-term. However, 3 small studies found a reduced response on long-term therapy in only a few patients.[7-9] Local injection of botulinum A toxin has been tried in refractory essential tremor. Benzodiazepines, and antimuscarinic or dopaminergic antiparkinsonian drugs may be effective in some forms of tremor.[1] Other drugs that have shown some benefit include gabapentin and topiramate.[1-4,10] Many other drugs have been tried, but there is little evidence to support their use.[10] In very severe disabling cases, surgery (thalamotomy or deep brain stimulation) may have to be considered.

1. Habib-ur-Rehman. Diagnosis and management of tremor. *Arch Intern Med* 2000; **160:** 2438–44.
2. Louis ED. Essential tremor. *N Engl J Med* 2001; **345:** 887–91.
3. Lyons K, *et al.* Benefits and risks of pharmacological treatments for essential tremor. *Drug Safety* 2003; **26:** 461–81.
4. Pahwa R, Lyons KE. Essential tremor: differential diagnosis and current therapy. *Am J Med* 2003; **115:** 134–42.
5. Benito-León J, Louis ED. Clinical update: diagnosis and treatment of essential tremor. *Lancet* 2007; **369:** 1152–4.
6. Koller WC, Royse VL. Efficacy of primidone in essential tremor. *Neurology* 1986; **36:** 121–4.
7. Koller WC, Vetere-Overfield B. Acute and chronic effects of propranolol and primidone in essential tremor. *Neurology* 1989; **39:** 1587–8.
8. Calzetti S, *et al.* Clinical and computer-based assessment of long-term therapeutic efficacy of propranolol in essential tremor. *Acta Neurol Scand* 1990; **81:** 392–6.
9. Sasso E, *et al.* Primidone in the long-term treatment of essential tremor: a prospective study with computerized quantitative analysis. *Clin Neuropharmacol* 1990; **13:** 67–76.
10. Zesiewicz TA, *et al.* Practice parameter: therapies for essential tremor: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2005; **64:** 2008–20. Also available at: http://www.neurology.org/cgi/reprint/64/12/2008.pdf (accessed 10/01/08)

Betaxolol Hydrochloride

(BANM, USAN, rINNM) ⊗

ALO-1401-02; Betaksolol Hidroklorür; Betaksololihydrokloridi; Betaksololio hidrochloridas; Bétaxolol, chlorhydrate de; Betaxolol-hidroklorid; Betaxolol-hydrochlorid; Betaxololhydroklorid; Betaxololi hydrochloridum; Hidrocloruro de betaxolol; SL-75212-10. 1-{4-[2-(Cyclopropylmethoxy)ethyl]phenoxy}-3-isopropylaminopropan-2-ol hydrochloride.

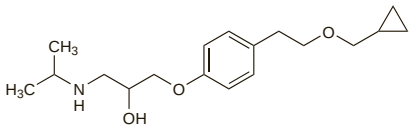
Бетаксолола Гидрохлорид

$C_{18}H_{29}NO_3$,HCl = 343.9.

CAS — 63659-18-7 (betaxolol); 63659-19-8 (betaxolol hydrochloride).

ATC — C07AB05; S01ED02.

ATC Vet — QC07AB05; QS01ED02.



(betaxolol)

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

Ph. Eur. 6.2 (Betaxolol Hydrochloride). A white or almost white crystalline powder. Very soluble in water; freely soluble in alcohol; soluble in dichloromethane. Protect from light.

USP 31 (Betaxolol Hydrochloride). A white crystalline powder. Freely soluble in water, in alcohol, in chloroform, and in methyl alcohol. pH of a 2% solution in water is between 4.5 and 6.5. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p.1226.

Interactions

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

Pharmacokinetics

Betaxolol is completely absorbed from the gastrointestinal tract and undergoes only minimal first-pass metabolism, resulting in a high oral bioavailability of about 90%. It has high lipid solubility. Betaxolol is about 50% bound to plasma proteins. It crosses the placenta and is distributed into breast milk where higher concentrations have been achieved than in maternal blood. The plasma elimination half-life of betaxolol ranges from 14 to 22 hours. The primary route of elimination is via hepatic metabolism and urinary excretion; only about 15% is excreted in the urine as unchanged drug.

Pregnancy and breast feeding. The pharmacokinetics of betaxolol were investigated in the perinatal period in 28 pregnant hypertensive patients receiving doses of 10 to 40 mg daily.[1] Pharmacokinetic values were similar to those seen in non-pregnant patients. Umbilical-cord concentrations were similar to maternal blood concentrations and showed a negative correlation between concentration in cord blood and timing of the last dose of betaxolol. Thus the betaxolol concentration in neonates can be considerably reduced by stopping maternal drug use 16 to 18 hours before birth. The blood-betaxolol half-life in the neonates ranged from 14.8 to 38.5 hours. The mean apparent half-life in infants with gestational age less than 36 weeks was about 32% higher than in full-term neonates. Betaxolol concentrations in milk and/or colostrum were determined in 3 mothers. In all samples the milk-to-blood ratio was greater than 2.

1. Morselli PL, *et al.* Placental transfer and perinatal pharmacokinetics of betaxolol. *Eur J Clin Pharmacol* 1990; **38:** 477–83.

Uses and Administration

Betaxolol is a cardioselective beta blocker (p.1225). It is reported to lack intrinsic sympathomimetic activity and to have little membrane-stabilising activity.

Betaxolol is used as the hydrochloride in the management of hypertension (p.1171), angina pectoris (p.1157), and glaucoma (p.1873).

In **hypertension** betaxolol hydrochloride is given in an initial oral dose of 10 mg once daily, which may be doubled if necessary after 1 to 2 weeks. Doses above 20 mg daily do not usually give additional benefit, but up to 40 mg daily has been tolerated. Similar doses are used in **angina pectoris**.

An initial dose of 5 mg daily is suggested for elderly patients. Reduced dosages should also be used in patients with severe renal impairment (see below).

Eye drops containing the equivalent of 0.25 or 0.5% betaxolol as the hydrochloride are instilled twice daily to reduce raised intra-ocular pressure in ocular hypertension and open-angle **glaucoma**.

◊ General references.

1. Buckley MM-T, *et al.* Ocular betaxolol: a review of its pharmacological properties, and therapeutic efficacy in glaucoma and ocular hypertension. *Drugs* 1990; **40:** 75–90.

Administration in renal impairment. The clearance of betaxolol is reduced in patients with renal impairment and the dose may therefore need to be reduced. Licensed US product information recommends an initial dose of betaxolol hydrochloride 5 mg daily in patients with severe renal impairment or on dialysis; the dose may be increased by 5 mg every 2 weeks, to a maximum of 20 mg daily.

Speech disorders. A 50-year-old man who had stuttered since childhood obtained striking improvement in his stuttering when he was given betaxolol 20 mg daily for essential hypertension.[1]

1. Burris JF, *et al.* Betaxolol and stuttering. *Lancet* 1990; **335:** 223.

Preparations

BP 2008: Betaxolol Eye Drops, Solution; Betaxolol Eye Drops, Suspension; ***USP 31:*** Betaxolol Ophthalmic Solution; Betaxolol Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Betasel; Tonobexol; ***Austral.:*** Betoptic; Betoquin; ***Austria:*** Betoptic; Kerlone; ***Belg.:*** Betoptic; Kerlone; ***Braz.:*** Betoptic; Presmin; ***Canad.:*** Betoptic; ***Chile:*** Bemaz; Beof; Betoptic; ***Cz.:*** Betalmic; Betaxa; Betoptic; Lokren; ***Denm.:*** Betoptic; Kerlon†; ***Fin.:*** Betoptic; Kerlon; ***Fr.:*** Betoptic; Kerlone; ***Ger.:*** Betoptima; Kerlone; ***Gr.:*** Armament; Betoptic; Eifel; Kerlone; Pertaxol†; ***Hong Kong:*** Betoptic; ***Hung.:*** Betoptic; Lokren; ***India:*** Optipres; ***Indon.:*** Betoptima; Optibet; ***Irl.:*** Betoptic; ***Israel:*** Betoptic; Kerlone; ***Ital.:*** Betoptic; Kerlon; ***Jpn:*** Kerlong; ***Malaysia:*** Betac; Betoptic; Kerlone; ***Mex.:*** Beofta†; Betoptic; BTX-HA Ofteno; ***Neth.:*** Betoptic; Kerlon; ***Norw.:*** Betoptic; ***NZ:*** Betoptic; ***Philipp.:*** Betoptic; Kerlone; ***Pol.:*** Betabion; Betoptic; Lokren; Optibetol; ***Port.:*** Bertocil; Betaglau; Betoptic; Davixolol; ***Rus.:*** Betac (Бетак); Betoptic (Бетоптик); Lokren (Локрен); ***S.Afr.:*** Betoptic; ***Singapore:*** Betac; Betoptic; Kerlone; ***Spain:*** Betoptic; ***Swed.:*** Betoptic; Kerlon†; ***Switz.:*** Betoptic; Kerlon†; ***Thai.:*** Betoptic; ***Turk.:*** Betoptic; ***UK:*** Betoptic; ***USA:*** Betoptic; Kerlone; ***Venez.:*** Betaxol; Betoptic.

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

Bévantolol, Chlorhydrate de; Bevantololhydroklorid; Bevantololi Hydrochloridum; Bevantololihydrokloridi; CI-775; Hidrocloruro de bevantolol; NC-1400. 1-(3,4-Dimethoxyphenethylamino)-3-*m*-tolyloxypropan-2-ol hydrochloride.

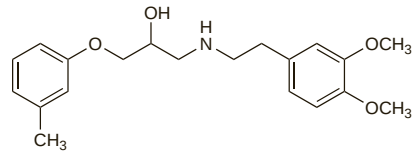
Бевантолола Гидрохлорид

$C_{20}H_{27}NO_4$,HCl = 381.9.

CAS — 59170-23-9 (bevantolol); 42864-78-8 (bevantolol hydrochloride).

ATC — C07AB06.

ATC Vet — QC07AB06.



(bevantolol)

Profile

Bevantolol is a cardioselective beta blocker (p.1225). It is reported to lack significant intrinsic sympathomimetic activity but has weak membrane-stabilising properties and also has vasodilator activity. It has been given orally as the hydrochloride in the management of hypertension and angina pectoris.

◊ References.

1. Frishman WH, *et al.* Bevantolol: a preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in hypertension and angina pectoris. *Drugs* 1988; **35:** 1–21.

Bezafibrate *(BAN, USAN, rINN)*

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

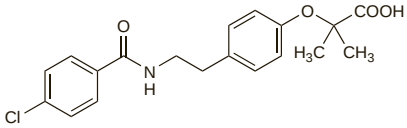
Безафибрат

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