2. van Heyningen C. Drug-induced acute autoimmune hepatitis during combination therapy with atorvastatin and ezetimibe. *Ann Clin Biochem* 2005; **42:** 402–4.
3. Stolk MF, *et al.* Severe hepatic side effects of ezetimibe. *Clin Gastroenterol Hepatol* 2006; **4:** 908–11.

Effects on the pancreas. Pancreatitis has been reported[1] in patients taking ezetimibe. In one case,[2] acute pancreatitis developed 2 weeks after starting ezetimibe and resolved when the drug was stopped, suggesting an immunological cause.

1. Adverse Drug Reactions Advisory Committee (ADRAC). Drug induced pancreatitis. *Aust Adverse Drug React Bull* 2006; **25:** 22. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0612.pdf (accessed 30/05/08)
2. Ahmad I, *et al.* Ezetimibe-induced acute pancreatitis. *South Med J* 2007; **100:** 409–10.

Effects on skeletal muscle. Muscle disorders such as myalgia and myopathy are well known to occur with lipid regulating drugs such as statins and fibrates and have also been reported with ezetimibe, both alone,[1,2] and when added to treatment with statins;[1,3] rhabdomyolysis has also occurred, but is rare in patients taking ezetimibe alone. Up to August 2005, the Australian Adverse Drug Reactions Advisory Committee[4] had received 44 reports of muscle disorders with ezetimibe, including myalgia, muscle cramp, weakness and pain; in 5 of these cases a statin was also being taken.

1. Simard C, Poirier P. Ezetimibe-associated myopathy in monotherapy and in combination with a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor. *Can J Cardiol* 2006; **22:** 141–4.
2. Havranek JM, *et al.* Monotherapy with ezetimibe causing myopathy. *Am J Med* 2006; **119:** 285–6.
3. Fux R, *et al.* Ezetimibe and statin-associated myopathy. *Ann Intern Med* 2004; **140:** 671–2.
4. Adverse Drug Reactions Advisory Committee (ADRAC). Ezetimibe and muscle disorders. *Aust Adverse Drug React Bull* 2005; **24:** 15. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0508.pdf (accessed 30/05/08)

Interactions

Colestyramine reduces the absorption of ezetimibe and should not be given at the same time of day. Ciclosporin has been reported to increase the plasma concentration of ezetimibe (see below) and patients receiving both drugs should be carefully monitored; the effect may be greater in patients with severe renal impairment. An increased INR has been reported in patients given ezetimibe and oral anticoagulants.

Ciclosporin. Pharmacokinetic studies[1] have shown that plasma-ezetimibe concentrations are higher in renal transplant patients taking ciclosporin than in historical controls, and there has been a report[2] of a supratherapeutic response to ezetimibe in a heart transplant patient taking ciclosporin. Ezetimibe causes a small increase in plasma-ciclosporin concentrations,[3] but the clinical relevance of this is not clear.

1. Bergman AJ, *et al.* Interaction of single-dose ezetimibe and steady-state cyclosporine in renal transplant patients. *J Clin Pharmacol* 2006; **46:** 328–36.
2. Koshman SL, *et al.* Supratherapeutic response to ezetimibe administered with cyclosporine. *Ann Pharmacother* 2005; **39:** 1561–5.
3. Bergman AJ, *et al.* Effects of ezetimibe on cyclosporine pharmacokinetics in healthy subjects. *J Clin Pharmacol* 2006; **46:** 321–7.

Pharmacokinetics

Ezetimibe is rapidly absorbed when given orally and undergoes extensive conjugation in the small intestine and liver to an active glucuronide metabolite, which is the main circulating form. Both ezetimibe and the glucuronide are more than 90% bound to plasma proteins. Ezetimibe is excreted primarily in the faeces via bile and undergoes enterohepatic recycling; after an oral dose, about 78% is excreted in the faeces, mainly as ezetimibe, and about 11% is excreted in the urine, mainly as the glucuronide. The elimination half-life for both ezetimibe and the glucuronide is about 22 hours. Ezetimibe is distributed into breast milk in *rats*.

◊ Reviews

1. Kosoglou T, *et al.* Ezetimibe: a review of its metabolism, pharmacokinetics and drug interactions. *Clin Pharmacokinet* 2005; **44:** 467–94.

Uses and Administration

Ezetimibe is an inhibitor of intestinal sterol absorption and inhibits the absorption of cholesterol and plant sterols. It is used to reduce total cholesterol, low-density lipoprotein (LDL)-cholesterol, and apolipoprotein B in the management of hyperlipidaemias (below), and to reduce sitosterol and campesterol in patients with homozygous familial sitosterolaemia. It is given orally in a usual dose of 10 mg once daily.

◊ Reviews.

1. Sudhop T, von Bergmann K. Cholesterol absorption inhibitors for the treatment of hypercholesterolaemia. *Drugs* 2002; **62:** 2333–47.
2. Mauro VF, Tuckerman CE. Ezetimibe for management of hypercholesterolemia. *Ann Pharmacother* 2003; **37:** 839–48.

Hyperlipidaemias. Ezetimibe inhibits the absorption of dietary cholesterol[1] and, although there is a compensatory increase in cholesterol synthesis in the liver,[1] overall plasma LDL-cholesterol concentrations are reduced.[2] Ezetimibe may be used alone in the management of hyperlipidaemias (p.1169) but use with lipid regulating drugs that act by reducing cholesterol synthesis may produce additive effects. In patients already taking statins, addition of ezetimibe results in a further reduction in LDL-cholesterol,[3] which may increase the number of patients achieving lipid targets, or allow lower doses of statins to be used. However, the clinical relevance of this is unclear; a study[4] in patients with familial hypercholesterolaemia found no difference in the progression of carotid atherosclerosis (measured by intima-media thickness) in those given ezetimibe with simvastatin compared with those given simvastatin alone, despite a larger reduction in LDL-cholesterol. Similar effects on LDL-cholesterol have been reported[5] for ezetimibe with fibrates.

As well as inhibiting cholesterol absorption, ezetimibe also blocks the absorption of plant sterols such as campesterol and sitosterol, and may be effective in patients with sitosterolaemia,[6] an inherited disorder in which increased absorption of plant sterols leads to premature atherosclerosis.

1. Sudhop T, *et al.* Inhibition of intestinal cholesterol absorption by ezetimibe in humans. *Circulation* 2002; **106:** 1943–8.
2. Knopp RH, *et al.* Effects of ezetimibe, a new cholesterol absorption inhibitor, on plasma lipids in patients with primary hypercholesterolemia. *Eur Heart J* 2003; **24:** 729–41.
3. Pearson TA, *et al.* A community-based, randomized trial of ezetimibe added to statin therapy to attain NCEP ATP III goals for LDL cholesterol in hypercholesterolemic patients: the ezetimibe add-on to statin for effectiveness (EASE) trial. *Mayo Clin Proc* 2005; **80:** 587–95.
4. Kastelein JJP, *et al.* The ENHANCE Investigators. Simvastatin with or without ezetimibe in familial hypercholesterolemia. *N Engl J Med* 2008; **358:** 1431–43.
5. McKenney JM, *et al.* Safety and efficacy of long-term co-administration of fenofibrate and ezetimibe in patients with mixed hyperlipidemia. *J Am Coll Cardiol* 2006; **47:** 1584–7.
6. Salen G, *et al.* Ezetimibe effectively reduces plasma plant sterols in patients with sitosterolemia. *Circulation* 2004; **109:** 966–71.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Acotral; Alin; Alipas; Cerclerol; Cetrakam; Coracil; Ezetrol; Ixacor; Lipimibe; Nalecol; Sinterol; Trilip; Vadel; Zetia; ***Austral.:*** Ezetrol; ***Austria:*** Ezetrol; ***Belg.:*** Ezetrol; ***Braz.:*** Ezetrol; Zetia; ***Canad.:*** Ezetrol; ***Chile:*** Ezetrol; Zient; ***Cz.:*** Ezetrol; Zient; ***Denm.:*** Ezetrol; ***Fin.:*** Ezetrol; ***Fr.:*** Ezetrol; ***Ger.:*** Ezetrol; ***Gr.:*** Ezetrol; ***Hong Kong:*** Ezetrol; ***Hung.:*** Ezetrol; ***India:*** Ezetib; Ezzicad†; Imbibe; ***Indon.:*** Ezetrol; ***Irl.:*** Ezetrol; ***Israel:*** Ezetrol; ***Malaysia:*** Ezetrol; ***Mex.:*** Ezetrol; Zient; ***Neth.:*** Ezetrol; ***Norw.:*** Ezetrol; ***NZ:*** Ezetrol; ***Philipp.:*** Ezetrol; ***Port.:*** Ezetrol; ***Rus.:*** Ezetrol (Эзетрол); ***S.Afr.:*** Ezetrol; ***Singapore:*** Ezetrol; ***Spain:*** Ezetrol; ***Swed.:*** Ezetrol; ***Switz.:*** Ezetrol; ***Thai.:*** Ezetrol; ***UK:*** Ezetrol; ***USA:*** Zetia; ***Venez.:*** Ezetrol; Zetia; Zient.

Multi-ingredient: ***Arg.:*** Alipas Duo; Ampliar Duo; Ateroclar Duo; Labistatin Duo; Liparex Duo; Lipibec Duo; Liponorm Duo; Redusterol Duo; Torimibe; Vasotenal EZ; Vytorin; ***Austral.:*** Vytorin; ***Austria:*** Inegy; Vytorin; ***Braz.:*** Vytorin; Zetsim; ***Chile:*** Adacai; Vytorin; Zintrepid; ***Cz.:*** Inegy; ***Fr.:*** Inegy; ***Ger.:*** Inegy; ***Gr.:*** Inegy; Vytorin; ***Hong Kong:*** Vytorin; ***Hung.:*** Inegy; ***India:*** Zetitor†; ***Indon.:*** Vytorin; ***Irl.:*** Inegy; ***Ital.:*** Inegy; Vytorin; ***Malaysia:*** Vytorin; ***Mex.:*** Vytorin; Zintrepid; ***Neth.:*** Inegy; Vytorin; ***Norw.:*** Inegy; ***NZ:*** Vytorin; ***Philipp.:*** Vytorin; ***Port.:*** Inegy; ***Singapore:*** Vytorin; ***UK:*** Inegy; ***USA:*** Vytorin; ***Venez.:*** Adacai; Vytorin; Zintrepid.

Fasudil Hydrochloride *(rINNM)*

AT-877; Fasudil, Chlorhydrate de; Fasudili Hydrochloridum; HA-1077; Hidrocloruro de fasudil. Hexahydro-1-(5-isoquinolylsulfonyl)-1*H*-1,4-diazepine hydrochloride.

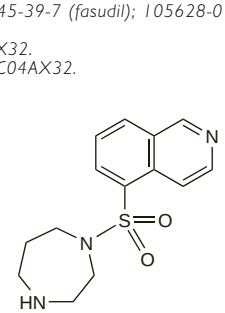
Фазудила Гидрохлорид

$C_{14}H_{17}N_3O_2S,HCl$ = 327.8.

CAS — 103745-39-7 (fasudil); 105628-07-7 (fasudil hydrochloride).

ATC — C04AX32.

ATC Vet — QC04AX32.



(fasudil)

Profile

Fasudil is a selective inhibitor of Rho-kinase, a protein kinase involved in contraction of vascular smooth muscle. Fasudil is used as the hydrochloride for its vasodilating properties in the management of cerebrovascular disorders including vasospasm after surgery for subarachnoid haemorrhage. It is under investigation for the treatment of angina pectoris, acute cerebral thrombosis, and pulmonary hypertension.

◊ References.

1. Shibuya M, *et al.* Effect of AT877 on cerebral vasospasm after aneurysmal subarachnoid hemorrhage: results of a prospective placebo-controlled double-blind trial. *J Neurosurg* 1992; **76:** 571–7.
2. Masumoto A, *et al.* Suppression of coronary artery spasm by the Rho-kinase inhibitor fasudil in patients with vasospastic angina. *Circulation* 2002; **105:** 1545–7.
3. Shimokawa H, *et al.* Anti-anginal effect of fasudil, a Rho-kinase inhibitor, in patients with stable effort angina: a multicenter study. *J Cardiovasc Pharmacol* 2002; **40:** 751–61.
4. Vicari RM, *et al.* Efficacy and safety of fasudil in patients with stable angina: a double-blind, placebo-controlled, phase 2 trial. *J Am Coll Cardiol* 2005; **46:** 1803–11.
5. Suzuki Y, *et al.* A postmarketing surveillance study of fasudil treatment after aneurysmal subarachnoid hemorrhage. *Surg Neurol* 2007; **68:** 126–31.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Eril†.

Felodipine *(BAN, USAN, rINN)*

Felodipiini; Felodipin; Felodipinas; Félodipine; Felodipino; Felodipinum; H-154/82. Ethyl methyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate.

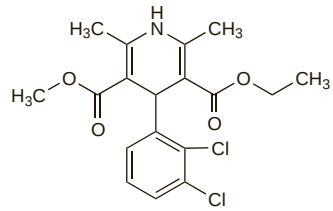
Фелодипин

$C_{18}H_{19}Cl_2NO_4$ = 384.3.

CAS — 72509-76-3; 86189-69-7.

ATC — C08CA02.

ATC Vet — QC08CA02.



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

Ph. Eur. 6.2 (Felodipine). A white or light yellow, crystalline powder. Practically insoluble in water; freely soluble in dehydrated alcohol, in acetone, in dichloromethane, and in methyl alcohol. Protect from light.

USP 31 (Felodipine). A light yellow to yellow, crystalline powder. Insoluble in water; freely soluble in acetone and in methyl alcohol; very slightly soluble in heptane. Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p.1350).

Interactions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p.1352).

Pharmacokinetics

Felodipine is almost completely absorbed from the gastrointestinal tract after oral doses but undergoes extensive first-pass metabolism, with a bioavailability of about 15% (range 10 to 25%). It is extensively metabolised in the gut and the liver and is excreted almost entirely as metabolites, about 70% of a dose being excreted in urine and the remainder in faeces. The terminal elimination half-life is reported to be about 11 to 16 hours after oral dosage with an immediate-release preparation, but longer with a modified-release formulation. Felodipine is about 99% bound to plasma proteins (mainly albumin).

◊ General reviews.

1. Dunselman PHJM, Edgar B. Felodipine clinical pharmacokinetics. *Clin Pharmacokinet* 1991; **21:** 418–30.

Uses and Administration

Felodipine is a dihydropyridine calcium-channel blocker with actions similar to those of nifedipine (p.1354). It is used in the management of hypertension (p.1171) and angina pectoris (p.1157).

Felodipine is given orally, generally in a modified-release formulation for use once daily in the morning. In **hypertension** the usual initial dose is 5 mg daily, adjusted as required; the usual maintenance dose is 2.5 to 10 mg daily and doses above 20 mg daily are not usually needed. In **angina** the usual initial dose is 5 mg daily increased if necessary to 10 mg daily.

Lower doses may be required in patients with hepatic impairment (see below) and in the elderly.

◊ Reviews.

1. Todd PA, Faulds D. Felodipine: a review of the pharmacology and therapeutic use of the extended release formulation in cardiovascular disorders. *Drugs* 1992; **44:** 251–77.
2. Walton T, Symes LR. Felodipine and isradipine: new calcium-channel-blocking agents for the treatment of hypertension. *Clin Pharm* 1993; **12:** 261–75.

Administration in hepatic impairment. In 9 patients with liver cirrhosis given felodipine 750 micrograms by intravenous infusion over 20 minutes and 10 mg orally as single doses on separate occasions the mean oral bioavailability was 17.1% which was not significantly different from published values in healthy subjects, but the maximum plasma concentrations were almost twice as high as normal, apparently due to reduced systemic clearance and volume of distribution.[1] The fact that bioavailability was not increased suggests that much pre-systemic metabolism takes place in the gut rather than the liver. Although increased adverse effects were not associated with the raised felodipine concentrations in this study it is recommended that therapy in cirrhotic patients begin at lower doses than in patients with normal liver function. US licensed product information recommends that an initial dose of 2.5 mg once daily should be used in patients with hepatic impairment.

1. Regårdh CG, *et al.* Pharmacokinetics of felodipine in patients with liver disease. *Eur J Clin Pharmacol* 1989; **36:** 473–9.

Preparations

USP 31: Felodipine Extended-Release Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Munobal; Plendil; ***Austral.:*** Agon†; Felodur; Plendil; ***Austria:*** Felodistad; Munobal; Plendil; ***Belg.:*** Plendil; Renedil; ***Braz.:*** Splendil; ***Canad.:*** Plendil; Renedil; ***Chile:*** Splendil; ***Cz.:*** Auronal; Felocor; Plendil; Presid; ***Denm.:*** Felodin; Hydac†; Plendil; Plendur; ***Fin.:*** Hydac; Plendil; ***Fr.:*** Flodil; ***Ger.:*** Felo-Puren; Felobeta; Felocor; Felogamma; Modip; Munobal; ***Gr.:*** Plendil; ***Hong Kong:*** Plendil; ***Hung.:*** Plendil; Presid; ***India:*** Felogard; ***Indon.:*** Nirmadil; Plendil; ***Irl.:*** Plendil; ***Israel:*** Penedil; ***Ital.:*** Feloday; Plendil; Prevex; ***Jpn:*** Splendil†; ***Malaysia:*** Plendil; ***Mex.:*** Fedin; Munobal; Plendil; ***Neth.:*** Plendil; Renedil; ***Norw.:*** Plendil; ***NZ:*** Felo; Plendil; ***Philipp.:*** Dilahex; Felim; Felop; Lodistad; Plendil; Versant; ***Pol.:*** Felohexal; Plendil; ***Port.:*** Mencor; Preslow; ***Rus.:*** Felodip (Фелодип); Plendil (Пленди́л); ***S.Afr.:*** Plendil; ***Singapore:*** Plendil; ***Spain:*** Fensel; Perfudal; Plendil; ***Swed.:*** Plendil; ***Switz.:*** Felodil; Munobal†; Plendil; ***Thai.:*** Felim; Felohexal; Feloten; Plendil; ***Turk.:*** Plendil; ***UK:*** Cardioplen; Felotens; Keloc; Neofel; Plendil; Vascalpha; ***USA:*** Plendil; ***Venez.:*** Munobal†; Plendil.

Multi-ingredient: ***Arg.:*** Nikion†; Triacor; ***Austral.:*** Triasyn; ***Austria:*** Triapin; Unimax; ***Belg.:*** Logimat; ***Cz.:*** Logimax†; Triasyn; Unimax†; ***Denm.:*** Logimax; ***Fin.:*** Logimax; Unimax; ***Fr.:*** Logimax; ***Ger.:*** Delmuno; Mobloc; Unimax; ***Gr.:*** Logimax; Triacor; Unitens; ***Hong Kong:*** Logimax; ***Hung.:*** Logimax; Triasyn; ***Irl.:*** Triapin; ***Israel:*** Logimax; ***Mex.:*** Logimax; Triacor; ***Neth.:*** Logimax; Triapin; Unimax; ***Philipp.:*** Logimax; Triapin; ***Port.:*** Unimax; ***Rus.:*** Logimax (Логимакс); ***S.Afr.:*** Tri-Plen; ***Spain:*** Logimax; ***Swed.:*** Logimax; ***Switz.:*** Logimax; Unimax; ***UK:*** Triapin; ***USA:*** Lexxel.

Fendiline Hydrochloride *(pINNM)*

Fendiline, Chlorhydrate de; Fendilini Hydrochloridum; Hidrocloruro de fendilina. *N*-(2-Benzhydrylethyl)-α-methylbenzylamine hydrochloride.

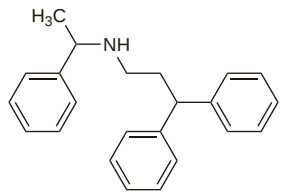
Фендилина Гидрохлорид

$C_{23}H_{25}N,HCl$ = 351.9.

CAS — 13042-18-7 (fendiline); 13636-18-5 (fendiline hydrochloride).

ATC — C08EA01.

ATC Vet — QC08EA01.



(fendiline)

Profile

Fendiline hydrochloride is a calcium-channel blocker used as a vasodilator in ischaemic heart disease.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Sensit†; ***Ger.:*** Sensit; ***Gr.:*** Sensit.

Fenofibrate *(BAN, rINN)*

Fenofibraatti; Fenofibrát; Fenofibrat; Fenofibratas; Fénofibrate; Fenofibrato; Fenofibratum; LF-178; Procetofen; Procetofene. Isopropyl 2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropionate.

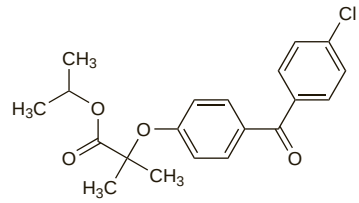
Фенофибрат

$C_{20}H_{21}ClO_4$ = 360.8.

CAS — 49562-28-9.

ATC — C10AB05.

ATC Vet — QC10AB05.



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

Ph. Eur. 6.2 (Fenofibrate). A white or almost white, crystalline powder. M.p. 79° to 82°. Practically insoluble in water; slightly soluble in alcohol; very soluble in dichloromethane. Protect from light.

USP 31 (Fenofibrate). A white or almost white, crystalline powder. M.p. 79° to 82°. Practically insoluble in water; slightly soluble in alcohol; very soluble in dichloromethane. Protect from light.

Adverse Effects and Precautions

As for Bezafibrate, p.1232.

Interactions

As for Bezafibrate, p.1232.

UK licensed product information for fenofibrate suggests that in patients taking oral anticoagulants, the dose of anticoagulant should be reduced by about one-third when treatment with fenofibrate is started, and then adjusted gradually if necessary.

Pharmacokinetics

Fenofibrate is readily absorbed from the gastrointestinal tract when taken with food; absorption may be reduced if fenofibrate is given on an empty stomach, although this depends on the formulation (see Bioavailability, below). It is rapidly hydrolysed to its active metabolite fenofibric acid which is about 99% bound to plasma albumin. The plasma elimination half-life is about 20 hours. Fenofibric acid is excreted mainly in the urine, mainly as the glucuronide conjugate, but also as a reduced form of fenofibric acid and its glucuronide. It is not removed by haemodialysis.

◊ References.

1. Chapman MJ. Pharmacology of fenofibrate. *Am J Med* 1987; **83** (suppl 5B): 21–5.

Bioavailability. Fenofibrate is poorly soluble in water and has a low bioavailability when given orally.[1] Bioavailability is increased by food, particularly if there is a high fat content, and fenofibrate is therefore usually given with meals. Changes to the formulation, particularly with regard to the particle size, have been made to improve solubility,[1] with the aim of increasing bioavailability and reducing the influence of food. Micronisation improves bioavailability to a certain extent, and allows a lower dose to be given; 300 mg of non-micronised fenofibrate is usually considered equivalent to about 200 mg of the standard micronised form. Microcoating may further improve bioavailability,[2] but absorption is still affected by the presence of food.[3] Nanoparticle,[4] stabilised microparticle,[3] or semi-solid formulations,[5] however, appear to have a more consistent bioavailability and may be given with or without food.

1. Vogt M, *et al.* Dissolution enhancement of fenofibrate by micronization, cogrinding and spray-drying: comparison with commercial preparations. *Eur J Pharm Biopharm* 2008; **68:** 283–8.
2. Guichard JP, *et al.* A new formulation of fenofibrate: suprabioavailable tablets. *Curr Med Res Opin* 2000; **16:** 134–8.
3. Guivarc'h PH, *et al.* A new fenofibrate formulation: results of six single-dose, clinical studies of bioavailability under fed and fasting conditions. *Clin Ther* 2004; **26:** 1456–69.
4. Sauron R, *et al.* Absence of a food effect with a 145 mg nanoparticle fenofibrate tablet formulation. *Int J Clin Pharmacol Ther* 2006; **44:** 64–70.
5. Sonet B, *et al.* Randomised crossover studies of the bioequivalence of two fenofibrate formulations after administration of a single oral dose in healthy volunteers. *Arzneimittelforschung* 2002; **52:** 200–4.

Uses and Administration

Fenofibrate, a fibric acid derivative, is a lipid regulating drug with actions on plasma lipids similar to those of bezafibrate (p.1233).

It is used to reduce low-density lipoprotein (LDL)-cholesterol, total cholesterol, triglycerides, and apolipoprotein B, and to increase high-density lipoprotein (HDL)-cholesterol, in the management of hyperlipidaemias (p.1169), including type IIa, type IIb, type III, type IV, and type V hyperlipoproteinaemias.

Fenofibrate is given orally. It is usually given with food to improve bioavailability although this may not be necessary with all preparations (see Bioavailability, above). It is available in a range of formulations with differing bioavailabilities and the dose is therefore specific to the preparation.

Standard micronised formulations of fenofibrate are available as 67-mg capsules to be taken several times daily, or as 200- or 267-mg capsules for once daily dosage. The usual initial dose is 67 mg three times daily or 200 mg once daily; the dose may be reduced to 67 mg twice daily or increased to 67 mg four times daily or 267 mg once daily according to response.

Preparations with improved bioavailability may be given in doses of around 40 to 160 mg once daily.

Non-micronised formulations may also be available and are given in an initial dose of 200 to 300 mg daily in divided doses, adjusted according to response to between 200 and 400 mg daily; 100 mg of non-micronised fenofibrate is therapeutically equivalent to 67 mg of the standard micronised form.

The dose of fenofibrate should be reduced in renal impairment (see below). For the dose of fenofibrate in children, see also below.

◊ Reviews.

1. Keating GM, Croom KF. Fenofibrate: a review of its use in primary dyslipidaemia, the metabolic syndrome and type 2 diabetes mellitus. *Drugs* 2007; **67:** 121–53.

Administration in children. Experience with fenofibrate in children is limited and it should only be given under specialist advice. The dose depends on the formulation:

- For *standard micronised* fenofibrate the *BNFC* recommends that children are given the 67-mg capsule formulation. The oral dose is one 67-mg capsule per 20 kg body-weight daily for children aged 4 to 15 years; those aged 15 to 18 years may be given the adult dose (see above).
- *Non-micronised* fenofibrate is licensed for use in some countries in children from the age of 10 years, in an oral dose of 5 mg/kg daily.

Administration in renal impairment. A single-dose study[1] in patients with mild (creatinine clearance (CC) 30 to 50 mL/minute) or severe renal impairment (CC below 10 mL/minute or undergoing haemodialysis) found that the plasma elimination half-life of fenofibric acid was prolonged, with a range of 54 to 362 hours; no correlation was found between half-life and serum creatinine or CC. Fenofibrate metabolites were not removed by haemodialysis, and repeated dosing in patients undergoing regular haemodialysis led to significant accumulation of fenofibric acid.[1]

Fenofibrate is therefore not generally recommended in patients with severe renal impairment although UK licensed product information allows a dose of 134 mg of standard micronised fenofibrate daily for patients with CC between 20 and 60 mL/minute and 67 mg daily for patients with CC below 20 mL/minute. US licensed product information for improved bioavailability formulations suggests initial daily doses of about 40 to 50 mg (equivalent to about 67 mg of standard micronised fenofibrate) in patients with renal impairment, but contra-indicates use in those with severe impairment.

1. Desager JP, *et al.* Effect of hemodialysis on plasma kinetics of fenofibrate in chronic renal failure. *Nephron* 1982; **31:** 51–4.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Craveril; Fenobrate; Fenolip†; Lipidil†; Lipoplasmin†; Minuslip; Procetoken; Qualecon†; Sclerofin; ***Austral.:*** Lipidil; ***Austria:*** Fenolip; Lipcor; Lipsin; ***Belg.:*** Docfenofi; Fenofitop; Fenogal; Lipanthyl; ***Braz.:*** Lipanon; Lipidil; ***Canad.:*** Apo-Feno; Lipidil; ***Chile:*** Lipidil; ***Cz.:*** Apo-Feno; Febira; Fenofix; Grofibrat†; Hypolip†; Lipanthyl; Lipirex; Lipohexal; Suprelip; ***Fin.:*** Lipanthyl; ***Fr.:*** Fegenor; Lipanthyl; Lipirex; Secalip; ***Ger.:*** ClL; durafenat; Fenobeta; Fenofanton; Lipanthyl; Lipidil; Normalip pro; ***Gr.:*** Lipanthyl; Lipidil; Neo-Disterin; Planitrix†; Zerlubron†; ***Hong Kong:*** Apo-Feno-Micro; Fegenor; Lexemin; Lipanthyl; Qualipantyl; Trolip†; ***Hung.:*** Feno-Micro; Fenobrat; Lipanthyl†; Lipidil; ***India:*** Fenolip; Lipicard; ***Indon.:*** Evothyl; Felosma; Hyperchol; Lipanthyl; Trichol; Trolip; Yosenob; Zumafib; ***Irl.:*** Lipantil; ***Ital.:*** Fulcro; Lipanthyl†; Lipofene; Lipsin; Nolipax; Scleril; Tilene; Volutine†; ***Jpn:*** Tricor; ***Malaysia:*** Apo-Feno-Micro; Lexemin; Lipanthyl; ***Mex.:*** Controlip;