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.

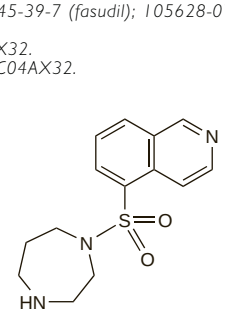
Фазудила Гидрохлорид

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

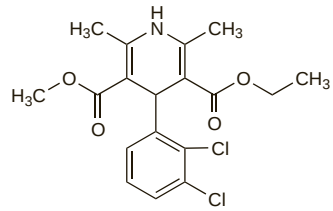
Фелодипин

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