Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Clorfibrase; ***Austria:*** Fibrolan; ***Braz.:*** Cauterex; Dermofibrin C†; Fibrabene; Fibrase; Fibrinase c/Cloranfenicol; Gino-Cauterex; Gino-Fibrase; Procutan†; ***Chile:*** Elase; ***Cz.:*** Fibrolan; ***Fr.:*** Elase; ***Ger.:*** Fibrolan†; ***Hung.:*** Fibrolan; ***Ital.:*** Elase†; ***Malaysia:*** Elase; ***Mex.:*** Fibrase; Fibrase SA; ***Pol.:*** Fibrolan; ***Switz.:*** Fibrolan.

Flecainide Acetate *(BANM, USAN, rINNM)*

Acetato de flecainida; Flécaïnide, acétate de; Flecainidi acetas; Flekainidacetat; Flekainid-acetát; Flekainidiasetaatti; Flekainido acetatas; R-818. *N*-(2-Piperidylmethyl)-2,5-bis(2,2,2-trifluoroethoxy)benzamide acetate.

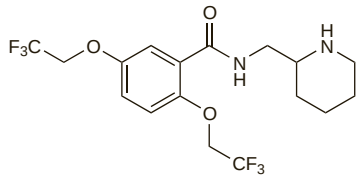
Флекаинида Ацетат

$C_{17}H_{20}F_6N_2O_3,C_2H_4O_2$ = 474.4.

CAS — 54143-55-4 (flecainide); 54143-56-5 (flecainide acetate).

ATC — C01BC04.

ATC Vet — QC01BC04.



(flecainide)

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

Ph. Eur. 6.2 (Flecainide Acetate). A white or almost white, very hygroscopic crystalline powder. Soluble in water and in dehydrated alcohol; freely soluble in dilute acetic acid; practically insoluble in dilute hydrochloric acid. A 2.5% solution in water has a pH of 6.7 to 7.1. Protect from light.

USP 31 (Flecainide Acetate). A white to slightly off-white crystalline powder; pK_a is 9.3. Soluble in water; freely soluble in alcohol.

Stability. Storage of an extemporaneously prepared flecainide syrup in a refrigerator led to crystallisation of the drug and a toxic dose being given.[1] It was suggested that oral liquid formulations of flecainide should be freshly reconstituted from a powder before each dose. However, other extemporaneous formulations have been reported[2,3] to be stable at room temperature and under refrigeration.

1. Stuart AG, *et al.* Is there a genetic factor in flecainide toxicity? *BMJ* 1989; **298:** 117–18.
2. Wiest DB, *et al.* Stability of flecainide acetate in an extemporaneously compounded oral suspension. *Am J Hosp Pharm* 1992; **49:** 1467–70.
3. Allen LV, Erickson MA. Stability of baclofen, captopril, diltiazem hydrochloride, dipyridamole, and flecainide acetate in extemporaneously compounded oral liquids. *Am J Health-Syst Pharm* 1996; **53:** 2179–84.

Adverse Effects

The most common adverse effects caused by flecainide affect the CNS and include dizziness, visual disturbances, and lightheadedness. Nausea, vomiting, headache, tremor, peripheral neuropathy, ataxia, and paraesthesia may also occur. These effects are generally transient and respond to dosage reduction. Other adverse CNS effects that have been reported rarely include hallucinations, amnesia, confusion, depression, dyskinesias, and convulsions. Skin reactions, including rare cases of urticaria, have also occurred and there have been isolated cases of photosensitivity. Disturbances of liver function have been reported rarely. Corneal deposits, pulmonary fibrosis, and pneumonitis have occurred during long-term therapy. Cardiovascular effects are less common than those on the CNS, but can be serious and sometimes fatal. Ventricular tachyarrhythmias have been reported, particularly in patients with a history of ventricular tachyarrhythmias and taking high doses of flecainide. Chest pain and myocardial infarction have also occurred. Flecainide produced an increased mortality rate when it was assessed for the control of asymptomatic ventricular arrhythmias in patients who had previously suffered a myocardial infarction (see Cardiac Arrhythmias under Uses and Administration, below).

Incidence of adverse effects. In a report of the non-cardiac adverse effects of flecainide from 1 short-term and 3 longer-term studies,[1] the most common adverse effects during both short- and long-term studies were dizziness and visual disturbances, which occurred in about 30% of patients. Headache and nausea both occurred in about 10% of patients. Other adverse effects reported include dyspnoea, chest pain, asthenia, fatigue, and tremor. Therapy was stopped because of non-cardiac adverse effects in 10% of patients in the short-term trial, and in 6% of those in the chronic studies. A review of 60 studies using flecainide[2] reported that non-cardiac adverse effects (mainly gastrointestinal and CNS adverse effects) occurred in 12% of patients. The UK CSM stated in June 1991 that it had received reports of neurological (4 patients with sensory neuropathy, 2 with ataxia), corneal (2 with corneal deposits), and pulmonary (3 with pulmonary fibrosis and pneumonitis) reactions associated with the long-term use of flecainide.[3]

1. Gentzkow GD, Sullivan JY. Extracardiac adverse effects of flecainide. *Am J Cardiol* 1984; **53:** 101B–105B.
2. Hohnloser SH, Zabel M. Short- and long-term efficacy and safety of flecainide acetate for supraventricular arrhythmias. *Am J Cardiol* 1992; **70:** 3A–10A.
3. Committee on Safety of Medicines. Multi-system adverse reactions following long-term flecainide therapy. *Current Problems 31* 1991. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024449&RevisionSelectionMethod=LatestReleased (accessed 08/05/07)

Effects on the blood. Severe granulocytopenia believed to be related to flecainide occurred in a 66-year-old man 3 months after starting therapy.[1] Haematological findings suggested an immune-mediated reaction in which flecainide binds to normal neutrophils with subsequent recognition by specific antibodies resulting in enhanced destruction of mature granulocytes in peripheral blood and bone marrow.

1. Samlowski WE, *et al.* Flecainide-induced immune neutropenia: documentation of a hapten-mediated mechanism of cell destruction. *Arch Intern Med* 1987; **147:** 383–4.

Effects on the eyes. In addition to visual disturbance, symptomatic corneal deposits have been reported[1] in patients taking flecainide. A study[2] in 38 patients found small corneal deposits in 14.5%, but visual function tests were normal.

1. Ulrik H, *et al.* Corneal deposits associated with flecainide. *BMJ* 1991; **302:** 506–7.
2. Ikäheimo K, *et al.* Adverse ocular effects of flecainide. *Acta Ophthalmol Scand* 2001; **79:** 175–6.

Effects on the heart. Like most antiarrhythmics, flecainide can have proarrhythmic effects,[1] and severe ventricular arrhythmias have been reported,[2] including fatal ventricular fibrillation[3] in a neonate given flecainide for supraventricular tachycardia. There has also been a report[4] of torsade de pointes, although this is generally less common with class Ic than with class Ia antiarrhythmics. For reports of increased cardiac mortality in patients given flecainide for asymptomatic arrhythmias, see Cardiac Arrhythmias under Uses and Administration, below.

1. Herre JM, *et al.* Inefficacy and proarrhythmic effects of flecainide and encainide for sustained ventricular tachycardia and ventricular fibrillation. *Ann Intern Med* 1990; **113:** 671–6.
2. Falk RH. Flecainide-induced ventricular tachycardia and fibrillation in patients treated for atrial fibrillation. *Ann Intern Med* 1989; **111:** 107–11.
3. Ackland F, *et al.* Flecainide induced ventricular fibrillation in a neonate. *Heart* 2003; **89:** 1261.
4. Nogales Asensio JM, *et al.* Torsade-de-pointes in a patient under flecainide treatment: an unusual case of proarrhythmicity. *Int J Cardiol* 2007; **114:** e65–e67.

Effects on the liver. Elevated liver enzymes and jaundice, reversible on stopping treatment, have been reported rarely with flecainide.

Conjugated hyperbilirubinaemia with jaundice developed in a newborn infant after maternal treatment with flecainide for fetal supraventricular tachycardia.[1]

1. Vanderhal AL, *et al.* Conjugated hyperbilirubinemia in a newborn infant after maternal (transplacental) treatment with flecainide acetate for fetal tachycardia and fetal hydrops. *J Pediatr* 1995; **126:** 988–90.

Effects on the lungs. There have been reports[1-4] of interstitial pneumonitis associated with flecainide. See also under Incidence of Adverse Effects, above.

1. Akoun GM, *et al.* Flecainide-associated pneumonitis. *Lancet* 1991; **337:** 49.
2. Hanston P, *et al.* Flecainide-associated interstitial pneumonitis. *Lancet* 1991; **337:** 371–2.
3. Robain A, *et al.* Flecainide-associated pneumonitis with acute respiratory failure in a patient with the LEOPARD syndrome. *Acta Cardiol* 2000; **55:** 45–7.
4. Pesenti S, *et al.* Diffuse infiltrative lung disease associated with flecainide: report of two cases. *Respiration* 2002; **69:** 182–5.

Effects on mental state. Dysarthria and visual hallucinations were associated with elevated plasma concentration of flecainide (2500 nanograms/mL) in a patient.[1] A serial rise and fall in plasma-bilirubin concentration during flecainide therapy also suggested possible direct hepatotoxicity. There has also been a report[2] of paranoid psychosis in a patient receiving flecainide for neuropathic pain.

1. Ramhamadany E, *et al.* Dysarthria and visual hallucinations due to flecainide toxicity. *Postgrad Med J* 1986; **62:** 61–2.
2. Bennett MI. Paranoid psychosis due to flecainide toxicity in malignant neuropathic pain. *Pain* 1997; **70:** 93–4.

Effects on the nervous system. Peripheral neuropathy, reversible on stopping treatment, has been reported[1,2] in patients receiving flecainide long-term. The authors of one report[1] stated that, at the time (1992), the UK CSM had received 4 other reports possibly associated with flecainide and 3 reports of aggravation of pre-existing neuropathy;[1] not all cases were reversible.

1. Palace J, *et al.* Flecainide induced peripheral neuropathy. *BMJ* 1992; **305:** 810.
2. Malesker MA, *et al.* Flecainide-induced neuropathy. *Ann Pharmacother* 2005; **39:** 1580.

Lupus erythematosus. There has been a report[1] of a patient who developed painful eye movement during flecainide therapy. The pain resolved on withdrawal but recurred when flecainide was restarted, and was accompanied by lateral rectus spasm, a facial rash, and positive antinuclear factor, suggestive of lupus erythematosus.

1. Skander M, Isaacs PET. Flecainide, ocular myopathy, and antinuclear factor. *BMJ* 1985; **291:** 450.

Treatment of Adverse Effects

In oral overdosage with flecainide activated charcoal may be considered if the patient presents within 1 hour of ingestion. Treatment is largely symptomatic and supportive and may need to be continued for extended periods of time because of the long half-life and the possibility of non-linear elimination at very high doses. Haemodialysis or haemoperfusion are unlikely to enhance elimination.

Overdosage. Severe cardiovascular toxicity in flecainide overdosage may be resistant to pacing and inotropes, and hypoperfusion of the kidneys and liver may reduce the elimination of flecainide, prolonging the toxic effects. Gastric decontamination is of uncertain benefit; forced diuresis has been used,[1] but probably had a negligible effect, and haemodialysis and haemoperfusion are not effective.[2] Patients may therefore require intensive and prolonged supportive treatment,[1,3] and there have been reports of the use of extracorporeal membrane oxygenation,[4] cardiopulmonary bypass,[5,6] or intra-aortic balloon pumping,[7] to maintain organ perfusion and allow flecainide elimination to occur, with complete recovery in some cases.[3,4,6,7] There have been reports[8,9] of the successful use of intravenous hypertonic sodium bicarbonate, and it has been suggested that it may antagonise the sodium channel blockade produced by flecainide, as well as reversing the metabolic acidosis that commonly occurs.

1. Winkelmann BR, Leinberger H. Life-threatening flecainide toxicity: a pharmacodynamic approach. *Ann Intern Med* 1987; **106:** 807–14.
2. Braun J, *et al.* Failure of haemoperfusion to reduce flecainide intoxication: a case study. *Med Toxicol* 1987; **2:** 463–7.
3. Hanley NA, *et al.* Survival in a case of life-threatening flecainide overdose. *Intensive Care Med* 1998; **24:** 740–2.
4. Auzinger GM, Scheinkestel CD. Successful extracorporeal life support in a case of severe flecainide intoxication. *Crit Care Med* 2001; **29:** 887–90.
5. Yasui RK, *et al.* Flecainide overdose: is cardiopulmonary support the treatment? *Ann Emerg Med* 1997; **29:** 680–2.
6. Corkeron MA, *et al.* Extracorporeal circulatory support in near-fatal flecainide overdose. *Anaesth Intensive Care* 1999; **27:** 405–8.
7. Timperley J, *et al.* Flecainide overdose—support using an intra-aortic balloon pump. *BMC Emerg Med* 2005; **5:** 10.
8. Goldman MJ, *et al.* Sodium bicarbonate to correct widened QRS in a case of flecainide overdose. *J Emerg Med* 1997; **15:** 183–6.
9. Lovecchio F, *et al.* Hypertonic sodium bicarbonate in an acute flecainide overdose. *Am J Emerg Med* 1998; **16:** 534–7.

Precautions

Flecainide treatment should be started in hospital or under specialist supervision and pacing rescue should be available when it is used in patients with conduction defects. Its use is limited to serious or life-threatening arrhythmias and it should not be given to control asymptomatic arrhythmias especially in patients with a history of myocardial infarction (see Cardiac Arrhythmias under Uses and Administration, below). Flecainide has some negative inotropic activity and may precipitate or aggravate heart failure in patients with compromised left ventricular function; it should therefore be used with extreme caution, if at all, in patients with heart failure. Flecainide has been shown to increase the endocardial pacing threshold and should be used with caution in patients with pacemakers. Electrolyte imbalances should be corrected before starting flecainide therapy. Reduction of dosage may be necessary in patients with renal impairment; extreme caution is needed in patients with pronounced hepatic impairment.

Breast feeding. Flecainide is distributed into breast milk but there have been no reports of infant exposure. Flecainide 100 mg was given orally every 12 hours to 11 healthy women, beginning 1 day after delivery and continuing for 5 days.[1] The mean elim-

ination half-life of flecainide from milk was 14.7 hours, very similar to the plasma elimination half-life. The mean milk to plasma ratios on study days 2 to 5 were 3.7, 3.2, 3.5, and 2.6 respectively but it was considered that the risk to breast-fed infants of ingesting toxic amounts of flecainide in breast milk would be very low. In another woman[2] who had been taking flecainide 100 mg twice daily since before pregnancy for ventricular arrhythmias, the ratio was 1.57 on day 5 postpartum and 2.18 on day 7. The American Academy of Pediatrics considers[3] flecainide to be usually compatible with breast feeding.

1. McQuinn RL, *et al.* Flecainide excretion in human breast milk. *Clin Pharmacol Ther* 1990; **48:** 262–7.
2. Wagner X, *et al.* Coadministration of flecainide acetate and sotalol during pregnancy: lack of teratogenic effects, passage across the placenta, and excretion in human breast milk. *Am Heart J* 1990; **119:** 700–2.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/07/07)

Pregnancy. Flecainide crosses the placenta (see under Pharmacokinetics, below) and has been used for transplacental therapy of fetal cardiac arrhythmias (see under Uses and Administration, below). However, hyperbilirubinaemia was reported in an infant after maternal treatment with flecainide (see Effects on the Liver, above).

Interactions

Use of flecainide with other antiarrhythmics or arrhythmogenic drugs may increase the incidence of cardiac arrhythmias. Use with a beta blocker produces additive negative inotropic effects. Flecainide undergoes hepatic metabolism and its activity may be influenced by drugs that affect the enzymes responsible for its metabolism, including the cytochrome P450 isoenzyme CYP2D6.

Antiarrhythmics. *Amiodarone* increases the plasma-flecainide concentration when the two drugs are given together.[1] It has been recommended that the dose of flecainide should be reduced by about one-half, but because the effect of amiodarone differs widely between patients, plasma-flecainide concentrations should be monitored. The clearance of flecainide may be decreased by *quinidine* in patients who are extensive metabolisers, since quinidine inhibits the enzyme responsible for the metabolism of flecainide.[2] Cardiogenic shock and asystole occurred in 2 patients receiving flecainide when *verapamil* was added to their therapy.[3]

1. Shea P, *et al.* Flecainide and amiodarone interaction. *J Am Coll Cardiol* 1986; **7:** 1127–30.
2. Birgersdotter UM, *et al.* Stereoselective genetically-determined interaction between chronic flecainide and quinidine in patients with arrhythmias. *Br J Clin Pharmacol* 1992; **33:** 275–80.
3. Buss J, *et al.* Asystole and cardiogenic shock due to combined treatment with verapamil and flecainide. *Lancet* 1992; **340:** 546.

Antimalarials. *Quinine* has been reported[1] to inhibit metabolism of flecainide in healthy subjects without altering its renal elimination, resulting in a reduction of total clearance and prolongation of the elimination half-life.

1. Munafo A, *et al.* Altered flecainide disposition in healthy volunteers taking quinine. *Eur J Clin Pharmacol* 1990; **38:** 269–73.

Beta blockers. Use of flecainide and *propranolol* in healthy subjects increases the plasma concentration of both drugs. The negative inotropic effects of the two drugs on cardiac function are at most only additive, but combined treatment should be started with caution in patients with impaired left ventricular function.[1] Addition of *sotalol* to flecainide has produced profound bradycardia and AV block followed by cardiac arrest and death in a man with ventricular tachycardia.[2]

1. Holtzman JL, *et al.* The pharmacodynamic and pharmacokinetic interaction of flecainide acetate with propranolol: effects on cardiac function and drug clearance. *Eur J Clin Pharmacol* 1987; **33:** 97–9.
2. Warren R, *et al.* Serious interactions of sotalol with amiodarone and flecainide. *Med J Aust* 1990; **152:** 277.

Digoxin. For reference to an interaction between flecainide and digoxin leading to increased concentrations of digoxin, see Antiarrhythmics, under Interactions of Digoxin, p.1261.

Food. *Milk* feeds reduced the absorption of flecainide in an infant who required a dose of 40 mg/kg daily to control supraventricular tachycardias. When milk feeds were replaced by glucose, the serum-flecainide concentration increased from 990 to 1824 nanograms/mL. Milk-fed infants on high doses of flecainide should have the dose reduced if milk is stopped or reduced.[1]

1. Russell GAB, Martin RP. Flecainide toxicity. *Arch Dis Child* 1989; **64:** 860–2.

Histamine H_2-antagonists. *Cimetidine* has been reported to increase the bioavailability of flecainide in healthy subjects, probably due to a decrease in the metabolism of flecainide. Elimination half-life and renal clearance were unchanged.[1]

1. Tjandra-Maga TB, *et al.* Altered pharmacokinetics of oral flecainide by cimetidine. *Br J Clin Pharmacol* 1986; **22:** 108–10.

Pharmacokinetics

Flecainide is almost completely absorbed after oral doses and does not undergo extensive first-pass hepatic metabolism. Although absorption is not affected by food or antacids, milk may inhibit absorption in infants (see above). Flecainide is metabolised to 2 major metabolites, *m-O*-dealkylated flecainide and *m-O*-dealkylated lactam of flecainide; both may have some activity, but this is unlikely to be clinically significant. Metabolism of flecainide appears to involve the cytochrome P450 isoenzyme CYP2D6 and is subject to genetic polymorphism (see Metabolism, below). It is excreted mainly in the urine, about 30% as unchanged drug and the remainder as metabolites. About 5% is excreted in the faeces. Excretion of flecainide is decreased in renal impairment, heart failure, and in alkaline urine. Haemodialysis removes only about 1% of an oral dose as unchanged flecainide.

The therapeutic plasma concentration range is generally accepted as 200 to 1000 nanograms/mL. The elimination half-life of flecainide is about 20 hours and it is about 40% bound to plasma proteins.

Flecainide crosses the placenta and is distributed into breast milk.

Metabolism. Oxidative metabolism is an important route of flecainide elimination.[1] It is mediated by the cytochrome P450 isoenzyme CYP2D6, which shows genetic polymorphism. The mean elimination half-life of flecainide in poor metabolisers (5 to 10% of the population) was found to be 11.8 hours compared with 6.8 hours in extensive metabolisers and the amounts of a dose excreted as unchanged drug in the urine were 51% and 31% respectively. These differences in pharmacokinetics will not usually be of clinical importance. However, in patients with renal impairment who are poor metabolisers, special care should be taken with dosage adjustments.

1. Mikus G, *et al.* The influence of the sparteine-debrisoquin phenotype on the disposition of flecainide. *Clin Pharmacol Ther* 1989; **45:** 562–7.

Pregnancy. A study of the pharmacokinetics of flecainide, given to a mother during the third trimester of pregnancy for the treatment of fetal supraventricular tachycardia,[1] indicated that close to term flecainide crosses the placenta easily without accumulating in fetal blood, but with a high concentration in the amniotic fluid.

See also Effects on the Liver, above.

1. Bourget P, *et al.* Flecainide distribution, transplacental passage and accumulation in the amniotic fluid during the third trimester of pregnancy. *Ann Pharmacother* 1994; **28:** 1031–4.

Uses and Administration

Flecainide is a class Ic antiarrhythmic (p.1153) used for the treatment of severe symptomatic ventricular arrhythmias such as sustained ventricular tachycardia; for premature ventricular contractions or non-sustained ventricular tachycardia resistant to other therapy; and for severe symptomatic supraventricular arrhythmias (AV nodal reciprocating tachycardia, arrhythmias associated with the Wolff-Parkinson-White syndrome, and paroxysmal atrial fibrillation in the absence of left ventricular dysfunction).

Flecainide is given orally or intravenously as the acetate. Treatment should be started in hospital. Doses should be adjusted after 3 to 5 days and reduced once control has been achieved. A suggested therapeutic plasma concentration range is 200 to 1000 nanograms/mL.

In ventricular arrhythmias the usual initial oral dose of flecainide acetate is 100 mg twice daily; the maximum total dose is 400 mg daily although most patients will not need more than 300 mg daily. In supraventricular arrhythmias the usual initial oral dose is 50 mg twice daily and the maximum total dose is 300 mg daily.

For rapid control of arrhythmias flecainide acetate 2 mg/kg may be given intravenously over 10 to 30 minutes, to a maximum dose of 150 mg; the ECG should be monitored. If longer term parenteral therapy is necessary it is started with intravenous injection of 2 mg/kg over 30 minutes, as above, then continued by intravenous infusion of 1.5 mg/kg over the first hour, and 100 to 250 micrograms/kg per hour thereafter. The maximum cumulative dose in the first 24 hours should not exceed 600 mg. Infusion should not generally continue for more than 24 hours and oral therapy should be substituted as soon as possible.

The dose of flecainide should be reduced in renal impairment (see below).

For the use of flecainide in children, see below.

Flecainide has also been tried in the treatment of refractory neuropathic pain.

Administration. Flecainide is usually given orally or intravenously, but rapid and reliable absorption has been reported from a rectal solution in healthy subjects.[1] The mean time to achieve peak serum concentration was 0.67 hours and the mean bioavailability was 98%, compared with 1 hour and 78% for an oral solution and 4 hours and 81% for a tablet. The absorption of flecainide given rectally to 2 critically ill patients was good in one but poor in the other[2] and it was recommended that rectal dosage be reserved for patients unresponsive to maximal parenteral therapy and in whom the oral or nasogastric routes cannot be used.

1. Lie-A-Huen L, *et al.* Absorption kinetics of oral and rectal flecainide in healthy subjects. *Eur J Clin Pharmacol* 1990; **38:** 595–8.
2. Quattrocchi FP, Karim A. Flecainide acetate administration by enema. *DICP Ann Pharmacother* 1990; **24:** 1233–4.

Administration in children. Flecainide has been used successfully to treat arrhythmias in children,[1,2] and beneficial results have also been reported[3] with flecainide and sotalol together. US licensed product information recommends an initial oral dose of flecainide acetate 50 mg/m^2 daily in divided doses for those aged under 6 months and 100 mg/m^2 daily for those aged over 6 months; a dose of 200 mg/m^2 daily should not be exceeded.

The *BNFC* recommends the following doses of flecainide acetate:

- neonates: an **oral** dose of 2 mg/kg 2 or 3 times daily, adjusted according to response, or 1 to 2 mg/kg **intravenously** over 10 to 30 minutes, followed if necessary by continuous infusion at a rate of 100 to 250 micrograms/kg per hour until arrhythmia is controlled
- children aged 1 month to 12 years: an **oral** dose of 2 mg/kg 2 or 3 times daily, adjusted according to response to a maximum of 8 mg/kg or 300 mg daily, or 2 mg/kg **intravenously** over 10 to 30 minutes, followed if necessary by continuous infusion at a rate of 100 to 250 micrograms/kg per hour until arrhythmia is controlled (maximum cumulative dose 600 mg in 24 hours)
- children aged 12 to 18 years: as for adults (see Uses and Administration, above); the maximum oral dose should not exceed 300 mg daily

1. Perry JC, Garson A. Flecainide acetate for treatment of tachyarrhythmias in children: review of world literature on efficacy, safety, and dosing. *Am Heart J* 1992; **124:** 1614–21.
2. O'Sullivan JJ, *et al.* Digoxin or flecainide for prophylaxis of supraventricular tachycardia in infants? *J Am Coll Cardiol* 1995; **26:** 991–4.
3. Price JF, *et al.* Flecainide and sotalol: a new combination therapy for refractory supraventricular tachycardia in children <1 year of age. *J Am Coll Cardiol* 2002; **39:** 517–20.

Administration in renal impairment. The plasma elimination half-life for flecainide may be prolonged in patients with renal impairment[1-3] and doses should be reduced. For patients with a creatinine clearance equal to or less than 35 mL/minute per 1.73 m^2 licensed product information states that the initial oral dose of flecainide acetate should not exceed 100 mg daily and plasma concentrations should be monitored; intravenous doses should be halved.

Special care with dosage adjustments should be taken in patients with renal impairment who are also poor metabolisers (see under Metabolism, above).

1. Braun J, *et al.* Pharmacokinetics of flecainide in patients with mild and moderate renal failure compared with patients with normal renal function. *Eur J Clin Pharmacol* 1987; **31:** 711–14.
2. Forland SC, *et al.* Oral flecainide pharmacokinetics in patients with impaired renal function. *J Clin Pharmacol* 1988; **28:** 259–67.
3. Williams AJ, *et al.* Pharmacokinetics of flecainide acetate in patients with severe renal impairment. *Clin Pharmacol Ther* 1988; **43:** 449–55.

Cardiac arrhythmias. Flecainide has an established role in the management of ventricular and supraventricular arrhythmias (p.1160). It has been used in children (see above) and has also been successfully given to pregnant women (transplacental therapy) to treat fetal arrhythmias,[1,2] although there have been reports[3,4] of neonatal toxicity.

Use in patients with asymptomatic arrhythmias after myocardial infarction is not recommended since an increase in mortality was found in the Cardiac Arrhythmia Suppression Trial (CAST), in which flecainide[5-7] and the related class Ic antiarrhythmics encainide[5-7] and moracizine[8] were used in an attempt to reduce the risk of sudden death in post-infarction patients with premature ventricular contractions.

Flecainide has also been used in the diagnosis of Brugada syndrome.[9] This syndrome is characterised by syncope or aborted cardiac arrest due to ventricular tachycardia in the absence of organic heart disease, and is thought to be due to a deficiency in

the inward sodium current in cardiac cells. Flecainide, because of its sodium-channel blocking action, exaggerates this deficiency and the resulting ST-segment elevation, and aids in diagnosis; however, it may precipitate serious ventricular arrhythmias[10] and must not be used for treatment.

1. Simpson JM, Sharland GK. Fetal tachycardias: management and outcome of 127 consecutive cases. *Heart* 1998; **79:** 576–81.
2. Krapp M, *et al*. Flecainide in the intrauterine treatment of fetal supraventricular tachycardia. *Ultrasound Obstet Gynecol* 2002; **19:** 158–64.
3. Rasheed A, *et al*. Neonatal ECG changes caused by supratherapeutic flecainide following treatment for fetal supraventricular tachycardia. *Heart* 2003; **89:** 470.
4. Hall CM, Ward Platt MP. Neonatal flecainide toxicity following supraventricular tachycardia treatment. *Ann Pharmacother* 2003; **37:** 1343–4.
5. Task Force of the Working Group on Arrhythmias of the European Society of Cardiology. CAST and beyond: implications of the cardiac arrhythmias suppression trial. *Circulation* 1990; **81:** 1123–7. [Simultaneous publication occurred in *Eur Heart J* 1990; **11:** 194–9].
6. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med* 1989; **321:** 406–12.
7. Echt DS, *et al*. Mortality and morbidity in patients receiving encainide, flecainide, or placebo: The Cardiac Arrhythmia Suppression Trial. *N Engl J Med* 1991; **324:** 781–8.
8. The Cardiac Arrhythmia Suppression Trial II Investigators. Effect of the antiarrhythmic agent moricizine on survival after myocardial infarction. *N Engl J Med* 1992; **327:** 227–33.
9. Singleton CB, McGuire MA. The Brugada syndrome: a recently recognised genetic disease causing sudden cardiac death. *Med J Aust* 2000; **173:** 415–8.
10. Gasparini M, *et al*. Flecainide test in Brugada syndrome: a reproducible but risky tool. *Pacing Clin Electrophysiol* 2003; **26:** 338–41.

Pain. Class Ic antiarrhythmics such as flecainide are among the drugs that have been used as analgesic adjuvants in neuropathic pain (p.8), although the evidence for benefit with flecainide is limited. A positive response has been reported[1,2] in patients with severe pain due to nerve infiltration, but a controlled trial had to be stopped[3] when supplies of the drug were withdrawn after the finding of increased mortality in a study in post-infarction patients (CAST; see Cardiac Arrhythmias, above), and a later study[4] found that flecainide was effective in only a minority of patients with cancer pain. A small study[5] has suggested that flecainide may be effective in postherpetic neuralgia.

1. Dunlop R, *et al*. Analgesic effects of oral flecainide. *Lancet* 1988; **i:** 420–1.
2. Sinnott C, *et al*. Flecainide in cancer nerve pain. *Lancet* 1991; **337:** 1347.
3. Dunlop RJ, *et al*. Flecainide in cancer nerve pain. *Lancet* 1991; **337:** 1347.
4. Chong SF, *et al*. Pilot study evaluating local anesthetics administered systemically for treatment of pain in patients with advanced cancer. *J Pain Symptom Manage* 1997; **13:** 112–17.
5. Ichimata M, *et al*. Analgesic effects of flecainide on postherpetic neuralgia. *Int J Clin Pharmacol Res* 2001; **21:** 15–19.

Preparations

BP 2008: Flecainide Injection; Flecainide Tablets;
USP 31: Flecainide Acetate Tablets.

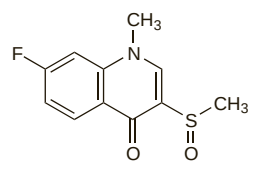
Proprietary Preparations (details are given in Part 3)
Arg.: Diondel; Tambocor†; ***Austral.:*** Flecatab; Tambocor; ***Austria:*** Aristocor; ***Belg.:*** Apocard; Tambocor; ***Canad.:*** Tambocor; ***Chile:*** Tambocor; ***Cz.:*** Tambocor; ***Denm.:*** Tambocor; ***Fin.:*** Tambocor; ***Fr.:*** Flecaine; ***Ger.:*** flecadura; Tambocor; ***Gr.:*** Tambocor; ***Hong Kong:*** Tambocor; ***Irl.:*** Tambocor; ***Israel:*** Tambocor; ***Ital.:*** Almarytm; ***Malaysia:*** Tambocor; ***Mex.:*** Tambocor; ***Neth.:*** Tambocor; ***Norw.:*** Tambocor; ***NZ:*** Tambocor; ***Philipp.:*** Tambocor; ***Port.:*** Apocard; ***S.Afr.:*** Tambocor; ***Singapore:*** Tambocor; ***Spain:*** Apocard; ***Swed.:*** Tambocor; ***Switz.:*** Tambocor; ***Thai.:*** Tambocor; ***UK:*** Tambocor; ***USA:*** Tambocor.

Flosequinan *(BAN, USAN, rINN)*

BTS-49465; Floséquinan; Flosequinán; Flosequinanum. 7-Fluoro-1-methyl-3-methylsulphinyl-4-quinolone.

Флозехинан

$C_{11}H_{10}FNO_2S$ = 239.3.
CAS — 76568-02-0.
ATC — C01DB01.
ATC Vet — QC01DB01.



Profile

Flosequinan is a direct-acting arteriovenous vasodilator that was used as an adjunct to the conventional treatment of heart failure, but was withdrawn from the market after findings of excess mortality.

◊ References.

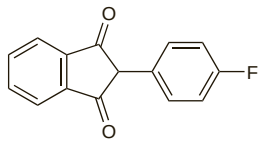
1. Kamali F, Edwards C. Possible role of metabolite in flosequinan-related mortality. *Clin Pharmacokinet* 1995; **29:** 396–403.

Fluindione *(rINN)*

Fluindiona; Fluindionum; Fluorindione; LM-123. 2-(4-Fluorophenyl)indan-1,3-dione.

Флуиндион

$C_{15}H_9FO_2$ = 240.2.
CAS — 957-56-2.



Profile

Fluindione is an oral indanedione anticoagulant with actions similar to those of warfarin (p.1425). It is used in the management of thromboembolic disorders (p.1187) but, as the indanediones are generally more toxic than warfarin (see Phenindione, p.1369), its use is limited.

The usual initial dose is 20 mg daily; the dose is then adjusted according to coagulation tests.

Preparations

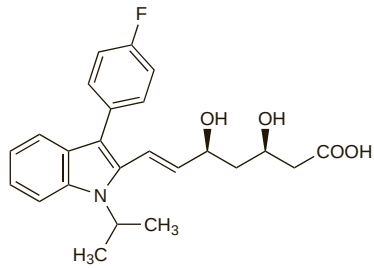
Proprietary Preparations (details are given in Part 3)
Fr.: Previscan.

Fluvastatin Sodium *(BANM, USAN, rINNM)*

Fluvastatina sódica; Fluvastatine sodique; Fluvastatinum natricum; Natrii Fluvastatinum; XU-62-320. Sodium (±)-(3*R**,5*S**,6*E*)-7-[3-(*p*-Fluorophenyl)-1-isopropylindol-2-yl]-3,5-dihydroxy-6-heptenoate.

Натрий Флувастатин

$C_{24}H_{25}FNNaO_4$ = 433.4.
CAS — 93957-54-1 (fluvastatin); 93957-55-2 (fluvastatin sodium).
ATC — C10AA04.
ATC Vet — QC10AA04.



(fluvastatin)

Pharmacopoeias. In *US.*
USP 31 (Fluvastatin Sodium). A white to pale yellow, brownish-pale yellow, or reddish-pale yellow, hygroscopic powder. Soluble in water, in alcohol, and in methyl alcohol. A 1% solution in water has a pH of 8.0 to 10.0. Store in airtight containers at a temperature not exceeding 40°. Protect from light and moisture.

Adverse Effects and Precautions

As for Simvastatin, p.1390.

Interactions

The interactions of statins with other drugs are described under simvastatin (p.1392). Fluvastatin is metabolised mainly by the cytochrome P450 isoenzyme CYP2C9 and does not have the same interactions with CYP3A4 inhibitors as simvastatin, although caution has been advised when such combinations are used. However, interactions may occur with inhibitors of CYP2C9, such as fluconazole; use with rifampicin, a CYP2C9 inducer, may reduce the bioavailability of fluvastatin by about 50%.

Pharmacokinetics

Fluvastatin is rapidly and completely absorbed from the gastrointestinal tract and undergoes extensive first-pass metabolism in the liver, its primary site of action. Metabolism is mainly by the cytochrome P450 isoenzyme CYP2C9, with only a small amount metabolised by CYP3A4. An absolute bioavailability of about 24% has been reported. It is more than 98% bound to plasma proteins. About 90% is excreted in the faeces, mainly as metabolites, with only about 6% being excreted in the urine.

◊ General reviews.

1. Scripture CD, Pieper JA. Clinical pharmacokinetics of fluvastatin. *Clin Pharmacokinet* 2001; **40:** 263–81.

Uses and Administration

Fluvastatin, a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (or statin), is a lipid regulating drug with actions on plasma lipids similar to those of simvastatin (p.1394). It is used to reduce total cholesterol, LDL-cholesterol, apolipoprotein B, and triglycerides, and to increase HDL-cholesterol, in the treatment of hyperlipidaemias (p.1169), including hypercholesterolaemias and combined (mixed) hyperlipidaemia (type IIa or IIb hyperlipoproteinaemias). It is also given as secondary prophylaxis for cardiovascular risk reduction (p.1164) in patients with ischaemic heart disease, including patients who have had a percutaneous coronary intervention.

Fluvastatin is given orally as the sodium salt, but doses are expressed in terms of the base; 21.06 mg of fluvastatin sodium is equivalent to about 20 mg of base. The usual initial dose is 20 to 40 mg of fluvastatin once daily in the evening. This may be increased, if necessary, at intervals of 4 weeks or more, up to 80 mg daily, in two divided doses or as a once-daily modified-release preparation; patients requiring a large reduction in LDL-cholesterol may be started on the 80 mg daily dose. A dose of 80 mg daily may also be used in patients who have had a percutaneous coronary intervention.

For the use of fluvastatin in children, see below.

◊ References.

1. Langtry HD, Markham A. Fluvastatin: a review of its use in lipid disorders. *Drugs* 1999; **57:** 583–606.
2. Corsini A, *et al*. Fluvastatin: clinical and safety profile. *Drugs* 2004; **64:** 1305–23.
3. Winkler K, *et al*. Risk reduction and tolerability of fluvastatin in patients with the metabolic syndrome: a pooled analysis of thirty clinical trials. *Clin Ther* 2007; **29:** 1987–2000.
4. McDonald KJ, Jardine AG. The use of fluvastatin in cardiovascular risk management. *Expert Opin Pharmacother* 2008; **9:** 1407–14.

Administration in children. Fluvastatin may be used in the management of children aged 10 to 16 years with heterozygous familial hypercholesterolaemia.[1] US licensed product information recommends an initial oral dose of 20 mg once daily, increased as required, at intervals of 6 weeks, to a maximum dose of 80 mg daily in 2 divided doses or as a once-daily modified-release preparation.

1. van der Graaf A, *et al*. Efficacy and safety of fluvastatin in children and adolescents with heterozygous familial hypercholesterolaemia. *Acta Paediatr* 2006; **95:** 1461–6.

Preparations

USP 31: Fluvastatin Capsules.

Proprietary Preparations (details are given in Part 3)
Arg.: Lescol; ***Austral.:*** Lescol; Vastin; ***Austria:*** Lescol; ***Belg.:*** Lescol; ***Braz.:*** Lescol; ***Canad.:*** Lescol; ***Cz.:*** Lescol; ***Denm.:*** Canef; Lescol; ***Fin.:*** Canef; Lescol; ***Fr.:*** Fractal; Lescol; ***Ger.:*** Cranoc; LOCOL; ***Gr.:*** Hovalin; Lescol; ***Hong Kong:*** Lescol; ***Hung.:*** Lescol; Lochol; ***Indon.:*** Lescol; ***Irl.:*** Lescol; ***Israel:*** Lescol; ***Ital.:*** Lescol; Lipaxan; Primesin; ***Jpn:*** Lochol; ***Malaysia:*** Lescol; ***Mex.:*** Canef†; Lescol; ***Neth.:*** Canef; Lescol; Vaditon; ***Norw.:*** Lescol; ***NZ:*** Lescol†; ***Philipp.:*** Lescol; ***Pol.:*** Lescol; ***Port.:*** Canef; Cardiol; Lescol; ***Rus.:*** Lescol (Лескол); ***S.Afr.:*** Lescol; ***Singapore:*** Lescol; ***Spain:*** Digaril; Lescol; Liposit; Lymetel; Princess Prolib†; Vaditon; ***Swed.:*** Canef; Lescol; ***Switz.:*** Lescol; Primesin; ***Thai.:*** Lescol; ***Turk.:*** Lescol; ***UK:*** Lescol; ***USA:*** Lescol; ***Venez.:*** Lescol†.