A study in 12 patients with chronic stable angina[1] showed that after treatment for one week with isosorbide dinitrate 30 mg two or three times daily, treadmill-walking time was longer throughout a 5-hour testing period compared with placebo. In contrast, after treatment for one week with isosorbide dinitrate 30 mg four times daily, treadmill-walking time was prolonged at 1 hour but not at 3 or 5 hours. These results support the concept that clinical efficacy of isosorbide dinitrate is maintained if given in a dose schedule which provides a nitrate-free or a low-nitrate period.

The effect of sublingual isosorbide dinitrate in patients receiving chronic therapy with isosorbide dinitrate was evaluated in 24 patients with angina.[2] Sublingual use produced less reduction of aortic systolic pressure and left ventricular end-diastolic pressure and less dilatation of coronary artery diameter in patients who received chronic isosorbide dinitrate therapy compared with patients not receiving chronic therapy.

1. Parker JO, *et al.* Effect of intervals between doses on the development of tolerance to isosorbide dinitrate. *N Engl J Med* 1987; **316:** 1440–4.
2. Naito H, *et al.* Effects of sublingual nitrate in patients receiving sustained therapy of isosorbide dinitrate for coronary artery disease. *Am J Cardiol* 1989; **64:** 565–68.

Oedema. Reports of ankle oedema associated with isosorbide dinitrate therapy in 3 patients with heart failure.[1]

1. Rodger JC. Peripheral oedema in patients treated with isosorbide dinitrate. *BMJ* 1981; **283:** 1365–6.

Interactions

As for Glyceryl Trinitrate, p.1297.

Disopyramide. The effectiveness of sublingual isosorbide dinitrate was reduced in a patient taking disopyramide.[1] The interaction was considered to be due to diminished salivary secretions caused by the antimuscarinic action of disopyramide which inhibited the dissolution of the sublingual isosorbide dinitrate tablet.

1. Barletta MA, Eisen H. Isosorbide dinitrate-disopyramide phosphate interaction. *Drug Intell Clin Pharm* 1985; **19:** 764.

Pharmacokinetics

Like glyceryl trinitrate, isosorbide dinitrate is readily absorbed from the oral mucosa. Isosorbide dinitrate is also readily absorbed when given orally but owing to extensive first-pass metabolism in the liver and presystemic clearance its bioavailability is reduced. Isosorbide dinitrate is also absorbed through the skin from an ointment basis.

After sublingual doses, anti-anginal effect is apparent within 2 to 5 minutes and persists for about 1 to 2 hours. After oral dosage with conventional tablets, anti-anginal activity is present in less than 1 hour and lasts for 4 to 6 hours.

Isosorbide dinitrate is widely distributed with a large apparent volume of distribution. It is taken up by smooth muscle cells of blood vessels and the nitrate group is cleaved to inorganic nitrite and then to nitric oxide. It is also rapidly metabolised in the liver to the major active metabolites isosorbide 2-mononitrate and isosorbide 5-mononitrate (see Isosorbide Mononitrate, below).

After sublingual doses, isosorbide dinitrate has a plasma half-life of 45 to 60 minutes. Plasma half-lives of 20 minutes and 4 hours have been reported after intravenous and oral dosage, respectively. During prolonged use, the half-life is increased due to accumulation of the isosorbide 5-mononitrate metabolite which reduces hepatic isosorbide dinitrate extraction. Both primary metabolites have longer half-lives than the parent compound.

◊ References.

1. Abshagen U, *et al.* Pharmacokinetics and metabolism of isosorbide-dinitrate after intravenous and oral administration. *Eur J Clin Pharmacol* 1985; **27:** 637–44.
2. Straehl P, Galeazzi RL. Isosorbide dinitrate bioavailability, kinetics, and metabolism. *Clin Pharmacol Ther* 1985; **38:** 140–9.
3. Thadani U, Whitsett T. Relationship of pharmacokinetic and pharmacodynamic properties of the organic nitrates. *Clin Pharmacokinet* 1988; **15:** 32–43.
4. Schneider W, *et al.* Concentrations of isosorbide dinitrate, isosorbide-2-mononitrate and isosorbide-5-mononitrate in human vascular and muscle tissue under steady-state conditions. *Eur J Clin Pharmacol* 1990; **38:** 145–7.
5. Vogt D, *et al.* Pharmacokinetics and haemodynamic effects of ISDN following different dosage forms and routes of administration. *Eur J Clin Pharmacol* 1994; **46:** 319–24.
6. Bergami A, *et al.* Pharmacokinetics of isosorbide dinitrate in healthy volunteers after 24-hour intravenous infusion. *J Clin Pharmacol* 1997; **37:** 828–33.

Uses and Administration

Isosorbide dinitrate is a vasodilator with general properties similar to those of glyceryl trinitrate (p.1297). It is used in the management of angina pectoris (p.1157) and of heart failure (below). It has also been investigated in myocardial infarction (p.1175).

Isosorbide dinitrate may be given by the sublingual, oral, transdermal, or intravenous route.

In **angina** isosorbide dinitrate may be given as sublingual tablets or spray for the relief of an acute attack, although glyceryl trinitrate may be preferred because it has a faster onset of action. Isosorbide dinitrate may also be used before an activity or stress which might provoke an attack. The usual dose in acute angina is 2.5 to 10 mg sublingually. As an alternative, one to three sprays (1.25 mg/spray) may be directed under the tongue.

Isosorbide dinitrate is also used in the long-term management of angina in oral doses of 20 to 120 mg daily in divided doses according to the patient's needs. Increases in dosage should be gradual to avoid adverse effects. Up to 240 mg daily in divided doses may be necessary. Modified-release formulations may be used in equivalent doses. Transdermal preparations such as topical sprays or ointments may also be used.

Isosorbide dinitrate is given by intravenous infusion for unstable angina. The dose is titrated according to patient response; doses in the range of 2 to 12 mg/hour are usually suitable but up to 20 mg/hour may be necessary in some patients. The plastic used in the infusion equipment may adsorb isosorbide dinitrate (see Stability, above) and allowance may have to be made for this.

During percutaneous transluminal coronary angioplasty isosorbide dinitrate may be given by the intracoronary route to allow prolonged balloon inflation and to prevent or relieve coronary spasm. Only injections of isosorbide dinitrate which are approved for intracoronary use should be given by this route as preparations intended for normal intravenous use may contain additives that are harmful if injected into diseased coronary vessels. The usual dose is 1 mg as a bolus before balloon inflation. The maximum recommended dose is 5 mg within a 30-minute time period.

Isosorbide dinitrate is also used in the management of **heart failure**. It is given in doses of 5 to 10 mg sublingually every 2 to 3 hours, or in oral doses of 30 to 160 mg daily in divided doses. Oral doses of up to 240 mg daily may be required. It may also be given intravenously using the intravenous doses given above for angina. An oral combination preparation with hydralazine is also available for use in self-identified black patients. It is given in a dose of 20 mg of isosorbide dinitrate with 37.5 mg of hydralazine three times daily; the dose may be doubled if necessary.

Heart failure. Although direct-acting vasodilators do not have a major role in the management of chronic heart failure (p.1165) there is some evidence that use of hydralazine with isosorbide dinitrate may be of benefit,[1] although the effect on mortality is less than that seen with ACE inhibitors.[2] Subgroup analysis suggested that the effect might be greater in black patients, and a later study[3] in black patients found that addition of isosorbide dinitrate and hydralazine to standard therapy improved both morbidity and mortality.

1. Cohn JN, *et al.* Effect of vasodilator therapy on mortality in chronic congestive heart failure: results of a Veterans Administration Cooperative Study. *N Engl J Med* 1986; **314:** 1547–52.
2. Cohn JN, *et al.* A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med* 1991; **325:** 303–10.
3. Taylor AL, *et al.* African-American Heart Failure Trial Investigators. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N Engl J Med* 2004; **351:** 2049–57. Correction. *ibid.* 2005; **352:** 1276.

Non-cardiovascular disorders. Nitrates such as isosorbide dinitrate have been tried in conditions including anal fissure, erectile dysfunction, obstetric and gynaecological disorders, oesophageal motility disorders such as achalasia and spasm, and pain. Further details of these uses are given under Glyceryl Trinitrate (p.1298).

Preparations

BP 2008: Isosorbide Dinitrate Injection; Isosorbide Dinitrate Sublingual Tablets; Isosorbide Dinitrate Tablets;

USP 31: Isosorbide Dinitrate Chewable Tablets; Isosorbide Dinitrate Extended-release Capsules; Isosorbide Dinitrate Extended-release Tablets; Isosorbide Dinitrate Sublingual Tablets; Isosorbide Dinitrate Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Cortespasmo; Isoket; Isordil; ***Austral.:*** Isordil; Sorbidin; ***Austria:*** Cedocard; Hexanitrat; Iso Mack; Isoket; Vasorbate; ***Belg.:*** Cedocard; Isordil†; ***Braz.:*** Angil; Dilatrat†; Isocord†; Isorbid†; Isordil; ***Canad.:*** Apo-ISDN; Cedocard†; Novo-Sorbide; ***Cz.:*** Apo-ISDN†; Cardiket; Dinisan; Iso Mack; Isoket; Isopelet; Maycor†; ***Denm.:*** Cardopax; Iso Mack†; ***Fin.:*** Dinit; Nitrosid; ***Fr.:*** Isocard; Langoran; Risordan; ***Ger.:*** Diconpin; duranitrat†; Iso Mack†; Iso-Puren; Isoket; Isostenase†; Jenacard; Maycor†; Nitrosorbon; TD Spray Iso Mack; ***Gr.:*** Orbipront†; Pensordil; ***Hong Kong:*** Apo-ISDN; Iso Mack†; Isoket; Isordil†; Isorem; ***Hung.:*** Iso Mack†; Isoket†; ***Indon.:*** Anzidin; Isordil; Sorbitrate; ***Indon.:*** Cedocard; Farsorbid; Hapisor; Isoket; Isordil; Sorbidin; Vascardin; ***Irl.:*** Isoket; Isordil†; ***Israel:*** Cordil; Isocardide; Isoket; Isolong; Isotard†; ***Ital.:*** Carvasin; Diniket; Nitrosorbide; ***Jpn:*** Antup R; Nitorol; ***Malaysia:*** Apo-ISDN†; Isoket; Isordil†; Nitorol†; Sorbidin†; ***Mex.:*** Biderit; Debisor; Insucar; Isoket; Isorbid; ***Neth.:*** Cedocard; Isordil; ***Norw.:*** Sorbangil; ***NZ:*** Coronex†; ***Philipp.:*** Bideren; Isobar; Isoket; Isordil; Nitrosorbon; ***Pol.:*** Aerosonit; Cardonit; Isoket; Sorbonit; ***Port.:*** Flindix; Isoket; Isopront†; ***Rus.:*** Isoket (Изокет); Isolong (Изолонг)†; Kardiket (Кардикет); ***S.Afr.:*** Angi-Spray; Dinospray; Isoket; Isordil; ***Singapore:*** Apo-ISDN; Iso Mack†; Isobin†; Isoket; Isordil†; ***Spain:*** Iso; Isordil†; ***Swed.:*** Sorbangil; ***Switz.:*** Acordin; Esconitro†; Iso Mack; Isoket; Isosifar†; Sorbidilat; ***Thai.:*** Angitrit; Hartsorb; Iso Mack†; Isobinate; Isoket; Isordil; Isorem; Isotrate; Izo†; Sorbidin; Sornil; ***Turk.:*** Cardioket; Isordil; Nitrofix; ***UK:*** Angitak; Cedocard; Isoket; ***USA:*** Dilatrate; Isochron; Isordil; Sorbitrate†; ***Venez.:*** Isoket; Isomack; Isordil†.

Multi-ingredient: ***Austria:*** Viskenit; ***Ger.:*** Stenoptin†; ***USA:*** BiDil.

Isosorbide Mononitrate *(BAN, USAN, rINN)*

AHR-4698; BM-22145; IS-5-MN; Isosorbid mononitrát; Isosorbide, mononitrate d'; Isosorbide-5-mononitrate; Isosorbidi mononitras; Izosorbid Mononitrat; Izosorbido mononitratas; Izoszorbid-mononitrát; Mononitrato de isosorbida. 1,4:3,6-Dianhydro-D-glucitol 5-nitrate.

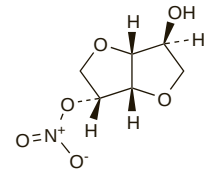
Изозорбида Мононитрат

$C_6H_9NO_6$ = 191.1.

CAS — 16051-77-7.

ATC — C01DA14.

ATC Vet — QC01DA14.



Pharmacopoeias. *Eur.* (see p.vii) and *US* include diluted isosorbide mononitrate.

Ph. Eur. 6.2 (Isosorbide Mononitrate, Diluted). A dry mixture of isosorbide mononitrate and lactose monohydrate or mannitol. The solubility of the diluted product depends on the diluent and its concentration. Protect from light.

Undiluted isosorbide mononitrate is a white or almost white, crystalline powder. Freely soluble in water, in alcohol, in acetone, and in dichloromethane.

USP 31 (Diluted Isosorbide Mononitrate). A dry mixture of isosorbide mononitrate with lactose or other suitable excipients to permit safe handling. Store in airtight containers between 20° and 30°.

Adverse Effects, Treatment, and Precautions

As for Glyceryl Trinitrate, p.1296.

Myalgia has been reported very rarely.

Interactions

As for Glyceryl Trinitrate, p.1297.

Pharmacokinetics

Isosorbide mononitrate is readily absorbed from the gastrointestinal tract. After oral doses of conventional tablets, peak plasma levels are reached in 30 minutes to 1 hour; onset of action occurs within 20 minutes and lasts for about 8 to 10 hours. Unlike isosorbide dinitrate, isosorbide mononitrate does not undergo first-pass hepatic metabolism and bioavailability is nearly 100%. Isosorbide mononitrate is widely distributed with a large apparent volume of distribution. It is taken up by smooth muscle cells of blood vessels and the nitrate group is cleaved to inorganic nitrite and then to nitric oxide. Isosorbide mononitrate is metabolised to inactive metabolites, including isosorbide and isosorb-

ide glucuronide. Only about 2% of isosorbide mononitrate is excreted unchanged in the urine. An elimination half-life of about 4 to 5 hours has been reported.

◊ References.

1. Taylor T, *et al.* Isosorbide 5-mononitrate pharmacokinetics in humans. *Biopharm Drug Dispos* 1981; **2:** 255–63.
2. Thadani U, Whitsett T. Relationship of pharmacokinetic and pharmacodynamic properties of the organic nitrates. *Clin Pharmacokinet* 1988; **15:** 32–43.
3. McClennen W, *et al.* The plasma concentrations of isosorbide 5-mononitrate (5-ISMN) administered in an extended-release form to patients with acute myocardial infarction. *Br J Clin Pharmacol* 1995; **39:** 704–8.
4. Hutt V, *et al.* Evaluation of the pharmacokinetics and absolute bioavailability of three isosorbide-5-mononitrate preparations in healthy volunteers. *Arzneimittelforschung* 1995; **45:** 142–5.
5. Baxter T, Eadie CJ. Twenty-four hour plasma profile of sustained-release isosorbide mononitrate in healthy volunteers and in patients with chronic stable angina: two open label trials. *Br J Clin Pharmacol* 1997; **43:** 333–5.

Uses and Administration

Isosorbide mononitrate is an active metabolite of the vasodilator isosorbide dinitrate and is used in the long-term management of angina pectoris (p.1157) and heart failure (p.1165). It has also been investigated in myocardial infarction (below).

The usual oral dose is 20 mg two or three times daily, although doses ranging from 20 to 120 mg daily have been given. Modified-release oral preparations have been developed for use in angina.

Myocardial infarction. Long-term management of myocardial infarction (p.1175) can involve numerous drug therapies and some patients, for example those with myocardial ischaemia or poor left ventricular function, may require the long-term use of nitrates, although recent studies have thrown doubt on their routine use. In the GISSI-3 study[1] there was no significant benefit from the use of transdermal glyceryl trinitrate when assessed 6 weeks post-infarction and in the ISIS-4 study[2] oral isosorbide mononitrate apparently had no effect on 35-day mortality.

1. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. *Lancet* 1994; **343:** 1115–22.
2. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58 050 patients with suspected acute myocardial infarction. *Lancet* 1995; **345:** 669–85.

Termination of pregnancy. For mention of the use of isosorbide mononitrate to ripen the cervix before termination of pregnancy, see Obstetrics and Gynaecology, under Glyceryl Trinitrate, p.1298.

Variceal haemorrhage. For reference to the use of isosorbide mononitrate in the management of variceal haemorrhage, see under Glyceryl Trinitrate, p.1299.

Preparations

BP 2008: Isosorbide Mononitrate Tablets; Prolonged-release Isosorbide Mononitrate Tablets;
USP 31: Isosorbide Mononitrate Extended-Release Tablets; Isosorbide Mononitrate Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Cilatron; Isolan†; Medocor; Misordil†; Monoket; Monotrin; ***Austral.:*** Arsorb; Duride; Imdur; Imtrate; Isomonit; Monodur; ***Austria:*** Elantan; Epicordin; Isomonat; Mono Mack; Monoket; Myocardon mono; Olicardin; ***Belg.:*** Promocard†; ***Braz.:*** Cincordil; Coronar; Monocordil; Revange†; ***Canad.:*** Imdur; ***Chile:*** Ismo; Mono Mack†; Monopack; ***Cz.:*** Conpin; Effox†; Imdur†; Ismin; Mono Mack; Monosan; Monosor; Monotab; Olicard; Sorbimon; ***Denm.:*** Fem-Mono; Imdur; Isodur; ***Fin.:*** Imdur; Isangina; Ismexin; Ismox; Isosor; Ormox; ***Fr.:*** Monicor; ***Ger.:*** Coleb; Conpin; Corangin; duramonitat†; Elantan; IS 5 Mono; Ismanton; Ismo; Isomonit; Moni-Sanorania; Monit-Puren; Mono Acis†; mono corax; Mono Mack; Mono Wolff; Monobeta; Monoclair; Monolong; Mononitrat; Monopur; Monostenase†; Olicard; Orasorbil†; Sigacora†; Turimonit; ***Gr.:*** Angiova†; Dilavenil; G-Dil; Imdur; Isomon; Monoginal; Monoket; Monorythm; Monosordil; Nitramin; Nitrilan†; Procardol; ***Hong Kong:*** Corangin†; Elantan; Imdex; Imdur; Ismo†; Mono Mack†; Monocinque; ***Hung.:*** Cardisorb; Isospan; Mono Mack; Olicard; Rangin; Sorbimon†; ***India:*** 5-Mono; IHD; Ismo; Isomin; Monicor; Monocontin; Monosorbitrate; Monotrate; ***Indon.:*** Imdur; Isomonit; Monecto; Pentacard; ***Irl.:*** Elantan; Imdur; Isomel; Isomonit; Sormon; ***Israel:*** Monocord; Monolong; Mononit; ***Ital.:*** Duronitrin; Elan; Ismo; Kiton†; Leicester; Monocinque; Monoket; Nitrex†; Vasdilat; ***Malaysia:*** Duride; Elantan; Imdex; Imdur; Ismo; ***Mex.:*** Elantan; Imdur; Kenbrid; Mono Mack†; Monocorat; ***Neth.:*** Mono-Cedocard; Promocard; ***Norw.:*** Imdur; Ismo; Monoket; ***NZ:*** Corangin; Duride; Imtrate; Ismo; ***Philipp.:*** Angistad; Elantan; Imdur; Isomonit; Monosorb; ***Pol.:*** Effox; Isomonit; Izonit; Mono Mack; Monocard; Mononit; ***Port.:*** Amplexol†; Imdur; Ismo; Monoket; Mononitril; Monopront; Orasorbil; ***Rus.:*** Effox (Эфокс); Monisol (Монизол); Monocinque (Моночинкве); Monolong (Монолонг)†; Monosan (Моносан); Olicard Retard (Оликард Ретард); Pektrol (Пектрол); ***S.Afr.:*** Angitrate; Elantan; Imdur; Ismo; ***Singapore:*** Elantan; Imdex; Imdur; Ismo†; Vasotrate; ***Spain:*** Cardionil; Cardiovas; Coronur; Dolak; Isonitril; Pertil; Uniket; ***Swed.:*** Fem-Mono†; Imdur; Ismo; Isodur; Monoket; ***Switz.:*** Corangine; Ismo†; ***Thai.:*** Elantan; Imdex; Imdur; Ismo; Isopen; Mono Mack†; Monolin; Monotrate; Solotrate; ***Turk.:*** Isorat; Monodur; Monoket; Monolong; ***UK:*** Angeze; Chemydur; Cibral; Dynamin; Elantan; Imdur; Isib; Ismo; Isodur; Isotard; Isotrate†; MCR-50†; Modisal; Monigen; Monit†; Monomax; Monomil; Monosorb; Trangina; Xismox; Zemon; ***USA:*** Imdur; Ismo; Monoket; ***Venez.:*** Elantan; Ismo; Mono Mack.

Multi-ingredient: ***Braz.:*** Vasclin; ***India:*** Aspitrate†; Mono-A; Solosprin; ***UK:*** Imazin†.

Isradipine *(BAN, USAN, rINN)*

Isradipiini; Isradipin; Isradipinas; Isradipino; Isradipinum; Izradypina; PN-200-110. Isopropyl methyl 4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate.

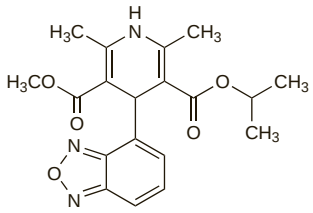
Израдипин

$C_{19}H_{21}N_3O_5$ = 371.4.

CAS — 75695-93-1.

ATC — C08CA03.

ATC Vet — QC08CA03.



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

Ph. Eur. 6.2 (Isradipine). A yellow crystalline powder. Practically insoluble in water; freely soluble in acetone; soluble in methyl alcohol. Protect from light.

USP 31 (Isradipine). A yellow fine crystalline powder. Protect from light.

Stability. An oral preparation of isradipine 1 mg/mL, prepared using the powder from capsules of isradipine suspended in syrup,[1] was stable when stored at 4° for up to 35 days after preparation.

1. MacDonald JL, *et al.* Stability of isradipine in an extemporaneously compounded oral liquid. *Am J Hosp Pharm* 1994; **51:** 2409–11.

Adverse Effects, Treatment, and Precautions

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

◊ In a multicentre study[1] involving 74 patients allocated to antihypertensive therapy with isradipine 2.5 to 10 mg twice daily, and 72 allocated to treatment with hydrochlorothiazide, adverse effects were reported in 44 of the isradipine group but only 29 of the thiazide group. Flushing, palpitation, and oedema were more common in patients receiving isradipine, while headache, dizziness, and dyspnoea were reported in both groups with similar frequency. In another study,[2] spontaneously reported adverse effects occurred less frequently in patients taking isradipine (18.4% of 103 patients) than in those taking amlodipine (33.3% of 102 patients). In particular, ankle oedema was less frequent, severe, and prolonged with isradipine than with amlodipine. A multicentre study[3] comparing isradipine and enalapril antihypertensive therapy reported adverse effects in 51% of 71 patients taking isradipine and 45% of 64 patients taking enalapril. The commonest side-effects with isradipine were dizziness (14%), oedema (10%), fatigue (9%), headache (9%), and pruritus (7%).

1. Carlsen JE, Køber L. Blood pressure lowering effect and adverse events during treatment of arterial hypertension with isradipine and hydrochlorothiazide. *Drug Invest* 1990; **2:** 10–16.
2. Hermans L, *et al.* At equipotent doses, isradipine is better tolerated than amlodipine in patients with mild-to-moderate hypertension: a double-blind, randomized, parallel-group study. *Br J Clin Pharmacol* 1994; **38:** 335–40.
3. Johnson BF, *et al.* A multicenter comparison of adverse reaction profiles of isradipine and enalapril at equipotent doses in patients with essential hypertension. *J Clin Pharmacol* 1995; **35:** 484–92.

Interactions

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

Cimetidine increases the bioavailability of isradipine and the dose of isradipine should be reduced by 50% in patients receiving both drugs.

Pharmacokinetics

Isradipine is almost completely absorbed from the gastrointestinal tract after oral doses but undergoes extensive first-pass metabolism; the bioavailability is reported to be 15 to 24%. Peak plasma concentrations occur about 2 hours after oral dosage. It is about 95% bound to plasma proteins. Isradipine is extensively metabolised in the liver, at least partly by the cytochrome P450 isoenzyme CYP3A4. About 70% of an oral dose is reported to be excreted as metabolites in urine, the remainder in faeces. The terminal elimination half-life is often stated to be about 8 hours although a value of less than 4 hours has also been reported.

◊ In single-dose and steady-state studies of the pharmacokinetics of isradipine in 9 hypertensive subjects using a specific high performance liquid chromatographic assay, isradipine was found to be rapidly absorbed with peak concentrations occurring 1.2 (steady state) to 1.5 (single dose) hours after dosing.[1] The mean terminal elimination half-life at steady state was 3.8 hours, suggesting that duration of action is likely to be short and that isradipine would need to be given at least twice daily. There was considerable interindividual variation in the pharmacokinetics. In an earlier study[2] in healthy subjects the effective half-life of isradipine was calculated to be 8.8 hours, but radiolabelled isradipine was used and the assay method might have been less specific for unchanged drug.

1. Shenfield GM, *et al.* The pharmacokinetics of isradipine in hypertensive subjects. *Eur J Clin Pharmacol* 1990; **38:** 209–11.
2. Tse FLS, Jaffe JM. Pharmacokinetics of PN 200-110 (isradipine), a new calcium antagonist, after oral administration in man. *Eur J Clin Pharmacol* 1987; **32:** 361–5.

Hepatic impairment. Systemic availability after a radiolabelled oral dose of isradipine 5 mg was no different at 15.6% in 7 patients with non-cirrhotic chronic liver disease from the value of 16.5% in 8 healthy subjects.[1] However, in 8 patients with cirrhosis of the liver availability was markedly increased to a mean of 36.9%; this was associated with decreased clearance (1.6 litres/minute, compared with 9.9 in controls). Terminal half-life, as measured after intravenous dosage, was greater at 11.9 hours in cirrhotic patients than the 5.1 hours seen in controls.

1. Cotting J, *et al.* Pharmacokinetics of isradipine in patients with chronic liver disease. *Eur J Clin Pharmacol* 1990; **38:** 599–603.

Uses and Administration

Isradipine is a dihydropyridine calcium-channel blocker with actions similar to those of nifedipine (p.1354). It is used in the treatment of hypertension (p.1171).

The usual initial dose of isradipine is 2.5 mg by mouth twice daily increased if necessary after 3 to 4 weeks to 5 mg twice daily. Some patients may require 10 mg twice daily. In elderly patients an initial dose of 1.25 mg twice daily may be preferable; a maintenance dose of 2.5 or 5 mg once daily may sometimes be sufficient. A reduced dose should also be considered in patients with hepatic or renal impairment (see below).

The dose of isradipine should be reduced in patients who are also taking cimetidine (see Interactions, above).

A modified-release preparation allowing once-daily dosing is available in some countries.

◊ Reviews.

1. Fitton A, Benfield P. Isradipine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in cardiovascular disease. *Drugs* 1990; **40:** 31–74.
2. Walton T, Symes LR. Felodipine and isradipine: new calcium-channel blocking agents for the treatment of hypertension. *Clin Pharm* 1993; **12:** 261–75.
3. Brogden RN, Sorkin EM. Isradipine: an update of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in the treatment of mild to moderate hypertension. *Drugs* 1995; **49:** 618–49.

Administration in hepatic or renal impairment. In patients with hepatic or renal impairment UK licensed product information recommends an initial dose of isradipine of 1.25 mg twice daily. The dose may be increased as required, but a maintenance dose of 2.5 or 5 mg once daily may be sufficient in some patients.

Preparations

BP 2008: Isradipine Tablets;
USP 31: Isradipine Capsules.

Proprietary Preparations (details are given in Part 3)

Arg.: Dynacirc†; ***Austria:*** Lomir; ***Belg.:*** Lomir; ***Braz.:*** Lomir; ***Chile:*** Dynacirc†; ***Cz.:*** Lomir; ***Denm.:*** Lomir; ***Fin.:*** Lomir; ***Fr.:*** Icaz; ***Ger.:*** Lomir; Vascal; ***Gr.:*** Lomir; ***Hong Kong:*** Dynacirc; ***Hung.:*** Lomir; ***Ital.:*** Clivoten; Esradin; Lomir; ***Malaysia:*** Dynacirc; ***Mex.:*** Dynacirc; ***Neth.:*** Lomir; ***Norw.:*** Lomir; ***NZ:*** Dynacirc; ***Philipp.:*** Icaz; ***Pol.:*** Lomir; ***Port.:*** Dilatol; Lomir; ***Rus.:*** Lomir (Ломир); ***S.Afr.:*** Dynacirc; ***Singapore:*** Dynacirc; ***Spain:*** Lomir; ***Swed.:*** Lomir; ***Switz.:*** Lomir; ***Thai.:*** Dynacirc; ***Turk.:*** Dynacirc; ***UK:*** Prescal; ***USA:*** Dynacirc; ***Venez.:*** Dynacirc†.