Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *US*.
Ph. Eur. 6.2 (Isoprenaline Sulphate). A white or almost white crystalline powder. Freely soluble in water; very slightly soluble in alcohol. A 5% solution in water has a pH of 4.3 to 5.5. Store in airtight containers. Protect from light.
USP 31 (Isoproterenol Sulfate). A white to practically white, odourless, crystalline powder. It gradually darkens on exposure to light and air. Soluble 1 in 4 of water; very slightly soluble in alcohol, in chloroform, in ether, and in benzene. A 1% solution in water has a pH of about 5. Solutions become pink to brownish-pink on standing exposed to air, and almost immediately so when made alkaline. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

As for Sympathomimetics, p.1407. Isoprenaline has almost exclusively beta-agonist properties but also stimulates the CNS; its main adverse effects include tachycardia and cardiac arrhythmias, palpitations, hypotension, tremor, headache, sweating, and facial flushing. Prolonged use of isoprenaline has been associated with swelling of the parotid glands.

Prolonged use of sublingual tablets may also cause severe damage to the teeth due to the acidic nature of the drug. Sublingual use or inhalation may colour the saliva or sputum red.

Increased mortality. For a discussion of the increased mortality and morbidity that has sometimes been observed in asthmatic patients using beta agonists and reference to an early epidemic associated with isoprenaline inhalers, see Fenoterol, p.1121.

Interactions

As for Sympathomimetics, p.1407. Due to the risk of arrhythmias, isoprenaline should not be used with other potent beta$_1$ agonists such as adrenaline.

Theophylline. For reports of increased theophylline clearance following use of isoprenaline, see p.1145.

Pharmacokinetics

As a result of sulfate conjugation in the gut, isoprenaline is considerably less active orally than after parenteral doses. It is absorbed through the oral mucosa and has accordingly been given sublingually, but absorption by this route remains very erratic. Isoprenaline in the body is resistant to metabolism by monoamine oxidase, but is metabolised by catechol-*O*-methyltransferase in the liver, lungs, and other tissues, the metabolite then being conjugated before excretion in the urine. Whereas the sulfate conjugate of isoprenaline is inactive the methylated metabolite exhibits weak activity.

After intravenous injection isoprenaline has a plasma half-life of about one to several minutes according to whether the rate of injection is rapid or slow; it is almost entirely excreted in the urine as unchanged drug and metabolites within 24 hours. A much slower onset of action and a more extended initial half-life has been found after oral dosage. Isoprenaline is reported to have a duration of action of up to about 2 hours after inhalation; it has been shown that a large proportion of an inhaled dose is swallowed.

◊ References.

1. Blackwell EW, *et al.* The fate of isoprenaline administered by pressurized aerosols. *Br J Pharmacol* 1970; **39:** 194P–195P.
2. Conolly ME, *et al.* Metabolism of isoprenaline in dog and man. *Br J Pharmacol* 1972; **46:** 458–72.
3. Blackwell EW, *et al.* Metabolism of isoprenaline after aerosol and direct intrabronchial administration in man and dog. *Br J Pharmacol* 1974; **50:** 587–91.
4. Reyes G, *et al.* The pharmacokinetics of isoproterenol in critically ill pediatric patients. *J Clin Pharmacol* 1993; **33:** 29–34.

Uses and Administration

Isoprenaline is a sympathomimetic (p.1408) that acts almost exclusively on beta-adrenergic receptors. It has a powerful stimulating action on the heart and increases cardiac output, excitability, and rate; it also causes peripheral vasodilatation and produces a fall in diastolic blood pressure and usually maintains or slightly increases systolic blood pressure. In addition, isoprenaline has bronchodilating properties. It also stimulates the CNS.

Isoprenaline has been used in a variety of cardiac disorders. It may be used for the temporary prevention or control of Stokes-Adams attacks and in severe bradycardia unresponsive to atropine, but use of a pacemaker is preferred. It has also been advocated as an adjunct for other cardiac disorders including shock (p.1183) and torsade de pointes (see Cardiac Arrhythmias, p.1160). It has been used in the diagnosis of congenital heart defects.

In the management of **cardiac disorders**, isoprenaline is usually given as the hydrochloride by slow intravenous infusion under ECG control. Infusion rates may range from 0.5 to 10 micrograms/minute depending on the clinical condition of the patient; 1 to 4 micrograms/minute may be adequate to correct bradycardia but rates of 4 to 8 micrograms/minute may be required for acute Stokes-Adams attacks. Isoprenaline hydrochloride can be given by intracardiac injection in extreme cases. It has also been given subcutaneously or intramuscularly in initial doses of 200 micrograms (as 1 mL of a 0.02% solution) and by slow intravenous injection in initial doses of 20 to 60 micrograms (as 1 to 3 mL of a 0.002% solution); doses are subsequently adjusted according to ventricular rate. Tablets of isoprenaline hydrochloride have been given orally or sublingually.

Isoprenaline has been used as a bronchodilator in the management of **reversible airways obstruction** but sympathomimetics with a selective action on beta$_2$ receptors, such as salbutamol, are now preferred (see Asthma, p.1108). It has been given as the sulfate or hydrochloride, usually by inhalation; sublingual tablets and intravenous injections have also been used.

Preparations

BP 2008: Isoprenaline Injection;
USP 31: Acetylcysteine and Isoproterenol Hydrochloride Inhalation Solution; Isoproterenol Hydrochloride and Phenylephrine Bitartrate Inhalation Aerosol; Isoproterenol Hydrochloride Inhalation Aerosol; Isoproterenol Hydrochloride Injection; Isoproterenol Hydrochloride Tablets; Isoproterenol Inhalation Solution; Isoproterenol Sulfate Inhalation Aerosol; Isoproterenol Sulfate Inhalation Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Ciapar†; Proterenal†; ***Austral.:*** Isuprel; ***Austria:*** Ingelan; ***Belg.:*** Isuprel; ***Cz.:*** Isuprel; ***Fr.:*** Isuprel; ***Ger.:*** Ingelan†; ***Gr.:*** Isuprel†; Saventrine†; ***Hung.:*** Isuprel†; ***India:*** Autohaler†; Isolin; ***Indon.:*** Isuprel; ***Irl.:*** Saventrine†; ***Israel:*** Isuprel; ***NZ:*** Isuprel; ***S.Afr.:*** Imuprel; Lenoprel†; ***Singapore:*** Isuprel†; Saventrine†; ***Spain:*** Aleudrina; ***Thai.:*** Isuprel; ***USA:*** Isuprel; Medihaler-Iso.

Multi-ingredient: ***Arg.:*** Zantril†; ***Austria:*** Ingelan; ***Ger.:*** Ingelan†; ***Mex.:*** Isobutil†; ***Port.:*** Prelus†; ***Spain:*** Aldo Asma; Frenal Compositum; ***USA:*** Norisodrine with Calcium Iodide.

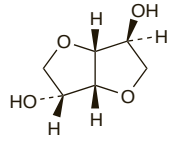
Isosorbide *(BAN, USAN, rINN)* ⊗

AT-101; Isosorbida; Isosorbidum; NSC-40725. 1,4:3,6-Dianhydro-D-glucitol.

Изосорбид

$C_6H_{10}O_4$ = 146.1.

CAS — 652-67-5.



Pharmacopoeias. In *Jpn.*
US includes Isosorbide Concentrate.
USP 31 (Isosorbide Concentrate). An aqueous solution containing 70.0 to 80.0% w/w of isosorbide. A colourless to slightly yellow liquid. Soluble in water and in alcohol. Store in airtight containers. Protect from light.

Profile

Isosorbide is an osmotic diuretic with properties similar to those of mannitol (p.1330). It is reported to cause less nausea and vomiting than other oral osmotic diuretics.

Isosorbide is used for short-term reduction of intra-ocular pressure in acute glaucoma or prior to surgery (p.1873). The usual oral dose is 1 to 3 g/kg 2 to 4 times daily. The onset of action is usually within 30 minutes and lasts for up to 5 or 6 hours.

Preparations

USP 31: Isosorbide Concentrate; Isosorbide Oral Solution.

Proprietary Preparations (details are given in Part 3)
Mex.: Biordyn; ***USA:*** Ismotic.

Isosorbide Dinitrate *(BAN, USAN, rINN)*

Dinitrato de isosorbida; ISDN; Isosorbid dinitrát; Isosorbiddinitrat; Isosorbide, dinitrate d'; Isosorbidi dinitras; Isosorbididinitraatti; Izosorbid Dinitrat; Izosorbido dinitratas; Izosorbidu diazotan; Izoszorbid-dinitrát; Sorbide Nitrate. 1,4:3,6-Dianhydro-D-glucitol 2,5-dinitrate.

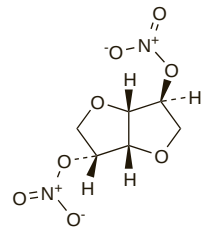
Изосорбида Динитрат

$C_6H_8N_2O_8$ = 236.1.

CAS — 87-33-2.

ATC — C01DA08; C05AE02.

ATC Vet — QC01DA08; QC05AE02.



Pharmacopoeias. In *Chin.* and *Jpn.*
Eur. (see p.vii), *Int.*, and *US* include diluted isosorbide dinitrate.
Ph. Eur. 6.2 (Isosorbide Dinitrate, Diluted). A dry mixture of isosorbide dinitrate and lactose monohydrate or mannitol. The solubility of the diluted product depends on the diluent and its concentration. Protect from light.
Undiluted isosorbide dinitrate is a fine, white or almost white, crystalline powder. Very slightly soluble in water; sparingly soluble in alcohol; very soluble in acetone.
USP 31 (Diluted Isosorbide Dinitrate). A dry mixture of isosorbide dinitrate (usually about 25%) with lactose, mannitol, or other suitable inert excipients, the latter being added to minimise the risk of explosion. It may contain up to 1% of a suitable stabiliser such as ammonium phosphate. It is an ivory-white, odourless powder. Store in airtight containers.
Undiluted isosorbide dinitrate occurs as white crystalline rosettes. Very slightly soluble in water; sparingly soluble in alcohol; very soluble in acetone; freely soluble in chloroform.

Handling. Undiluted isosorbide dinitrate may explode if subjected to percussion or excessive heat.

Stability. The loss of isosorbide dinitrate from solution during infusion was found to be 30% with PVC plastic intravenous infusion sets but negligible when polyolefin or glass delivery systems were used.[1] Another study reported a 23% decrease in isosorbide dinitrate concentration after 24 hours of storage at 21° in PVC containers; most of the loss occurred in the first 6 hours. Loss of potency was not noted when isosorbide dinitrate was stored under similar conditions in glass bottles or polyethylene, nylon, and polypropylene laminated bags.[2]

1. Kowaluk EA, *et al.* Drug loss in polyolefin infusion systems. *Am J Hosp Pharm* 1983; **40:** 118–19.
2. Martens HJ, *et al.* Sorption of various drugs in polyvinyl chloride, glass, and polyethylene-lined infusion containers. *Am J Hosp Pharm* 1990; **47:** 369–73.

Adverse Effects, Treatment, and Precautions

As for Glyceryl Trinitrate, p.1296.

Effects on the blood. Haemolysis occurred in 2 patients with G6PD deficiency during treatment with isosorbide dinitrate.[1]

1. Aderka D, *et al.* Isosorbide dinitrate-induced hemolysis in G6PD-deficient subjects. *Acta Haematol (Basel)* 1983; **69:** 63–4.

Headache. The most common adverse effect of nitrate therapy is headache which usually decreases after a few days. There has been a report[1] of a severe continuous unilateral headache with an oculosympathetic paresis on the same side associated with isosorbide dinitrate therapy.

1. Mueller RA, Meienberg O. Hemicrania with oculosympathetic paresis from isosorbide dinitrate. *N Engl J Med* 1983; **308:** 458–9.

Hypersensitivity. Laryngeal oedema developed on two occasions in a woman after the use of isosorbide dinitrate spray;[1] nifedipine was also given sublingually which on the second occasion caused a noticeable increase in the laryngeal swelling induced by the nitrate.

1. Silfvast T, *et al.* Laryngeal oedema after isosorbide dinitrate spray and sublingual nifedipine. *BMJ* 1995; **311:** 232.

Nitrate tolerance. Continuous use of organic nitrates is associated with tolerance to their haemodynamic effects; for an overview of nitrate tolerance, see under Precautions for Glyceryl Trinitrate, p.1297.

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.

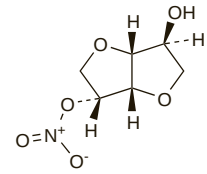
Изозорбида Мононитрат

$C_6H_9NO_6$ = 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-