Sorbidin

Isosorbide Dinitrate

PRODUCT INFORMATION

Composition

Isosorbide dinitrate (sorbide nitrate).

Actions

Antianginal, vasodilator.

Pharmacology

Isosorbide dinitrate is an organic nitrate ester. It has a slower time to onset of action, but longer duration of action, than glyceryl trinitrate. The longer duration of action is due, in part, to the drug having a longer elimination half-life than glyceryl trinitrate and to the fact that its mononitrated metabolites are pharmacologically active and have long elimination half-lives (see **Pharmacokinetics**).

Like other organic nitrate ester drugs, the principal action of isosorbide dinitrate is to relax vascular smooth muscle. Venodilation causes venous pooling which reduces venous return, left ventricular filling pressure and pulmonary artery and capillary pressures. Myocardial oxygen requirements are also reduced. Arteriolar dilation can result in a reduction in afterload. The clinical implication of these haemodynamic changes in patients with congestive heart failure can be an increase in cardiac output and a reduction in symptoms of pulmonary vascular congestion. Patients with angina pectoris attain relief through a reduction in myocardial oxygen requirements.

Nitrates may cause a redistribution of coronary blood flow to ischaemic areas by selectively dilating large coronary vessels or collateral vessels which may develop secondary to myocardial ischaemia.

Pharmacokinetics

An oral availability of at least 20% means that the oral route is effective in providing significant amounts of isosorbide dinitrate for systemic pharmacological effects. After chronic oral dosing at 6 hourly intervals, plasma levels of isosorbide dinitrate are greater than after single doses of the drug. This is associated with a reduced clearance of isosorbide dinitrate after chronic dosing.

An apparent terminal half-life of 1.1 to 1.3 hours has been reported for single oral and sublingual doses, and intravenous doses of isosorbide dinitrate. However, on monitoring plasma isosorbide dinitrate concentrations for up to 24 hours after chronic doses at 6 hourly intervals, a biexponential decay profile was reported with the first phase having a half-life of 1.1 hours and a second phase having a half-life of 7.7 hours. The first and faster half-life probably represents elimination of isosorbide dinitrate, while the second and slower half-life represents either protracted oral absorption or a redistribution of isosorbide dinitrate back from the peripheral tissues to the systemic circulation. The apparent disappearance half-lives of the 2- and 5-mononitrate metabolites are about 3 hours and 4 to 6 hours respectively.

There are no differences in plasma levels of isosorbide dinitrate after single oral doses of the drug in normal subjects and renal failure patients; but because isosorbide dinitrate and its mononitrate metabolites accumulate with chronic dosing, significant accumulation of the drug and its metabolites may occur, particularly in patients with hepatic and/or renal failure.

Indications

Treatment of angina pectoris (classic effort associated angina, chronic stable angina, vasospastic angina, variant angina, unstable angina and angina decubitus) and myocardial ischaemia due to ischaemic heart disease. The tablets are not intended to abort the acute anginal episode, but are useful in the prophylactic treatment of angina pectoris and myocardial ischaemia due to ischaemic heart disease.

An aid in the management of left ventricular failure, either alone or as part of the syndrome of congestive heart failure.

Contraindications

Patients with a confirmed diagnosis of isolated right ventricular failure, particularly in the setting of acute myocardial infarction and due to dominant right ventricular infarction.

Known hypersensitivity to isosorbide dinitrate, or a known idiosyncratic reaction to organic nitrate drugs.

Hypotension or uncorrected hypovolaemia, as the use of isosorbide dinitrate in such states could produce severe hypotension or shock.

Constrictive pericarditis and pericardial tamponade.

Severe anaemia or arterial hypoxaemia.

Intracranial hypertension.

Concurrent administration with sildenafil.

Warnings

As with other vasodilators, Sorbidin may cause paradoxical side effects in sensitive patients, which may increase ischaemia and may even lead to extension of myocardial damage and advanced congestive heart failure.

Acute myocardial infarction. Data supporting the use of nitrates during the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety. Management of acute left ventricular failure secondary to acute myocardial infarction depends on accurate diagnosis, and may require flow-directed cardiac catheterisation before institution of appropriate drug therapy.

Hypotension. Care must be taken to avoid the significant risk of a precipitous fall in blood pressure, particularly in patients with severe coronary or cerebral atherosclerosis or renal insufficiency. Isosorbide dinitrate may cause

faintness if taken while standing or sitting, and this hazard is of particular importance in patients not previously treated with the drug.

Withdrawal. Nitrate dependence is a potentially serious problem. In terminating treatment of patients with angina who are receiving isosorbide dinitrate, both the dosage and frequency of administration should be gradually reduced over a period of 2 weeks to prevent potential withdrawal reactions such as increased frequency of angina attacks.

Tolerance. During sustained therapy with isosorbide dinitrate, partial tolerance to the antianginal and circulatory effects may develop. Cross tolerance to other organic nitrates or nitrites may occur.

Precautions

In the treatment of acute or chronic cardiac failure, pulmonary capillary pressure should not be allowed to fall below 15 mm Hg or systolic blood pressure below the physiological range in normal or hypertensive patients. Systolic pressure should be preserved in patients with pre-existing hypotension in the range of 90 to 100 mm Hg.

Marked symptomatic, orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustment of either class of agents may be necessary.

Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

Tolerance to this drug and cross-tolerance to other nitrates and nitrites may occur.

Hypoxaemia. Arterial oxygen tension decreases after administration of glyceryl trinitrate in normal subjects and in patients with coronary artery disease, and therefore it is advised that isosorbide dinitrate should be used cautiously in hypoxic patients because a decrease in available oxygen may oppose the antianginal effect of isosorbide dinitrate.

Haemolytic anaemia. Isosorbide dinitrate has been reported to induce haemolytic anaemia in glucose-6-phosphate dehydrogenase deficient patients.

Relief of acute episodes of angina. Oral isosorbide dinitrate tablets should not be administered for rapid relief of the pain of angina.

Relief of left ventricular failure. If left ventricular filling pressures are not elevated at the time isosorbide dinitrate is administered, the drug may cause severe hypotension due to a reduction in cardiac output.

Impaired hepatic function. Isosorbide dinitrate is, in part, metabolised by the liver and therefore impairment of hepatic function may necessitate a reduction in dosage.

Impaired renal function. In patients with renal failure, the plasma concentrations of isosorbide dinitrate and its active metabolites after single oral doses of the drug are not different from those seen in subjects with normal renal function. Although only 5% of a single dose of isosorbide dinitrate is excreted in the urine as the mononitrate metabolites, it is possible that with chronic dosing of isosorbide dinitrate, renal impairment could cause clinically significant accumulation of the active mononitrate metabolites (see **Pharmacology - Pharmacokinetics**).

Use in Pregnancy (Risk Category: B1)

The safety of isosorbide dinitrate in pregnancy has not been established. The drug should not be administered to pregnant women unless, in the opinion of the physician, the probable clinical benefits outweigh the possible hazards.

Use in Lactation

It is not known whether isosorbide dinitrate or its metabolites are excreted in milk, or whether it has a harmful effect on the newborn. Therefore, it is not recommended for nursing mothers unless the expected benefits outweigh any potential risk.

Paediatric Use

As safety and efficacy have not been demonstrated for this age group, isosorbide dinitrate is not recommended for use in children.

Use in the Elderly

In general, the dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

Interactions

Patients receiving antihypertensive drugs or phenothiazines with nitrates should be observed for possible additive hypotensive effects.

Concomitant use with alcohol may cause hypotension due to enhanced vasodilatory effect of isosorbide dinitrate.

Caution should be observed when giving tricyclic antidepressants and anticholinergic agents concomitantly with isosorbide dinitrate, because these agents may potentiate the hypotensive effects of isosorbide dinitrate. NSAIDs may attenuate the effects of isosorbide dinitrate, considering similar reports for glyceryl trinitrate.

The use of β-adrenergic blocking agents may require a reduction in isosorbide dinitrate dosage if excessive hypotension is to be avoided.

Concurrent administration of nitrates and sildenafil can potentiate the vasodilatory effects of nitrates, with the potential result of serious side effects such as syncope or myocardial infarction. Therefore, sildenafil should not be given to patients already receiving isosorbide dinitrate therapy.

Adverse Reactions

Occasionally, individuals may exhibit marked sensitivity to the hypotensive effects of nitrates, even with the usual therapeutic dosage.

More common reactions

Nervous system. Headache, which may be temporary or persistent, is the most common adverse reaction in patients treated with isosorbide dinitrate; dizziness, especially postural.

Less common reactions

Cardiovascular. Cutaneous dilation with flushing; peripheral oedema.

Dermatological. Rash, exfoliative dermatitis.

Gastrointestinal. Nausea, vomiting.

Haematological. Haemolytic anaemia in patients with glucose-6-phosphate dehydrogenase deficient syndrome (see **Precautions**).

Serious or life-threatening reactions

Severe hypotension and bradycardia may be hazardous, particularly in patients with cerebral or coronary atherosclerosis. Reflex tachycardia may exacerbate ischaemic injury in patients with acute myocardial infarction.

Dosage and Administration

Tolerance to the anti-anginal effects (measured by exercise stress testing) and effects in heart failure of nitrates has been shown to be a major factor limiting efficacy and blunting the effect of sublingual nitroglycerin when nitrates are used either continuously (i.e. infusion, transdermal) or with any regular schedule of oral administration where dosing occurs every 8 hours or more often during a day. The development of tolerance can be altered (prevented or attenuated) by a non-continuous (intermittent or asymmetric) dosing schedule. In general, a nitrate-free interval of at least 10 to 12 hours every 24 hours is recommended to prevent tolerance.

Angina pectoris and myocardial ischaemia due to ischaemic heart disease. 5 to 30 mg four times daily. The average patient requires 10 mg four times daily.

Left ventricular failure (either alone or as part of the syndrome of congestive heart failure). In order to obtain full therapeutic effect, it is important that the dosage be individualised in accordance with each patient's needs, clinical response and haemodynamic monitoring. Sorbidin therapy should begin with the lowest effective dose and further adjusted as necessary, based on left ventricular performance. In the treatment of chronic left ventricular failure, the tablets may be used for maintenance therapy (20 to 40 mg four times daily or as needed).

Overdosage

Symptoms. Overdosage of isosorbide dinitrate may result in severe hypotension and reflex tachycardia. Headache may be an indication of excessive overdosage.

Treatment. Following recent ingestion of large numbers of isosorbide dinitrate tablets, gastric lavage and administration of oxygen with assisted respiration may be necessary. Hypotension and reflex tachycardia caused by overdosage can be treated by elevating the legs until the patient's condition stabilises. Since the duration of the haemodynamic effects following isosorbide dinitrate administration may be prolonged, additional corrective measures may be required. In that event, cautious administration of intravenous fluids or an α -adrenergic agonist (e.g. metaraminol) should be considered.

Presentation and Storage Conditions

Sorbidin, 10 mg tablet: white, normal convex, marked IS/10 on one side, α on reverse; 100's.

Store below 30°C.

Poison Schedule of the Medicine

S3 - Pharmacist Only Medicine

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