AUSTRALIAN PRODUCT INFORMATION – ISORDIL (ISOSORBIDE DINITRATE) TABLET AND SUBLINGUAL TABLET

1 NAME OF THE MEDICINE

Isosorbide dinitrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Isordil sublingual tablets contain 5 mg of isosorbide dinitrate.

Isordil oral tablets come in three strengths and contain 10mg, 30mg or 40mg of isosorbide dinitrate.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Isordil Sublingual Tablets: 5 mg (round, flat, pink, unmarked tablet)

Isordil Oral Tablets:

10 mg: (round, white, bi-convex tablet impressed with the company logo with a break bar on other side)
30 mg: (round, blue, bi-convex tablet, impressed with the company logo and a break bar on other side.)
40 mg: (round, green, bi-convex tablet, impressed with the company logo and a break bar on other side.)
* Currently not marketed

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Treatment of angina pectoris (classic effort associated angina, chronic stable angina, vaso-spastic angina, variant angina, unstable angina and angina decubitus) and myocardial ischaemia due to ischaemic heart disease, and an aid in the management of left ventricular failure, either alone or as part of the syndrome of congestive heart failure.

Sublingual

Prevention and treatment of angina pectoris and myocardial ischaemia due to ischaemic heart disease. Acute and chronic left ventricular failure, either alone or as part of the syndrome of congestive heart failure to improve cardiac performance and stabilise the patient's condition.

Oral

Relief of angina pectoris. It is not intended to abort the acute anginal episode, but is 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.

4.2 DOSE AND METHOD OF 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 8 hours every 24 hours is recommended to prevent tolerance.

Adult

Angina Pectoris and Myocardial Ischaemia Due to Ischaemic Heart Disease

The usual dose of sublingual isosorbide dinitrate for this indication is 5 to 10 mg every two to three hours for treatment of an angina pectoris attack or prophylactically in situations likely to provoke such attacks. The sublingual tablets may also be swallowed in doses of 5 to 10 mg for prevention of angina pectoris or to supplement the oral dosage form.

Oral tablets should be taken in doses of 5 to 30 mg four times daily, the average patient requiring 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 of sublingual and oral forms be individualised in accordance with each patient's needs, clinical response and haemodynamic monitoring. Isordil therapy should begin with the lowest effective dose and further adjusted as necessary, based on left ventricular performance. For treatment of acute left ventricular failure, the sublingual form of Isordil should be preferred. For the treatment of chronic left ventricular failure, initially the rapid acting sublingual form of Isordil should be administered to stabilise the patient's symptoms or to determine the magnitude of haemodynamic response; then it should be followed by the oral form for maintenance therapy.

The average recommended doses for acute and chronic left ventricular failure are the following:

Acute left ventricular failure

Sublingual tablet: 5 to 10 mg every two hours or as needed.

Chronic left ventricular failure

Initial dosage, sublingual tablet: 5 to 10 mg every two hours or as needed. Maintenance dosage, oral tablet: 20 to 40 mg four times daily or as needed.

4.3 CONTRAINDICATIONS

. In 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.

. Do not use isosorbide dinitrate in patients who are taking certain drugs for erectile dysfunction (phosphodiesterase inhibitors), such as sildenafil, tadalafil or vardenafil. Concomitant use can cause severe hypotension, syncope or myocardial ischemia.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

As with other vasodilators, Isordil 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 two 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.

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 90-100 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. Sublingual administration of isosorbide dinitrate tablets offers relatively fast relief.

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.

Use in hepatic impairment

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

Use in renal impairment

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 section 5.2 PHARMACOKINETIC PROPERTIES).

Use in the elderly

In general, 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.

Paediatric use

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

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Concurrent use of sildenafil can result in significant potentiation of the hypotensive effects of organic nitrates, such as isosorbide dinitrate, and is therefore contraindicated. Concomitant use of isosorbide dinitrate with phosphodiesterase inhibitors is contraindicated (See section 5.3 CONTRAINDICATIONS).

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 an enhanced vasodilatory effect of isosorbide dinitrate.

Caution should be observed when giving tricyclic antidepressants and anti-cholinergic agents concomitantly with isosorbide dinitrate because these agents may potentiate the hypotensive effects of isosorbide dinitrate. Non-steroidal anti-inflammatory drugs may attenuate the effects of isosorbide dinitrate, considering similar reports for glyceryl trinitrate.

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

Use in pregnancy – Pregnancy 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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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 system - cutaneous dilatation with flushing. Peripheral

oedema. Dermatological -rash, exfoliative dermatitis. Gastrointestinal - nausea, vomiting. Haematological - haemolytic anaemia in patients with glucose-6-phosphate dehydrogenase-deficient syndrome (See section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Clinical features: Overdosage of isosorbide dinitrate may result in severe hypotension and reflex tachycardia. Headache may be an indication of excessive dosage.

Management: 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 alpha-adrenergic agonist (e.g. Metaraminol) should be considered.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Antianginal, vasodilator.

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 also section 5.2 PHARMACOKINETIC PROPERTIES).

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 dilatation can result in a reduction in after-load. 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.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Isosorbide dinitrate is absorbed faster after sublingual administration than after oral administration.

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.

Half-life: An apparent terminal half life of 1.1 to 1.3 hours has been reported for single oral and sublingual doses and IV 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 4-6 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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The 5 mg tablets also contain the following excipients: cellulose-microcrystalline, erythrosine, lactose monohydrate, magnesium stearate, starch-maize.

The 10mg, 30 mg and 40 mg tablets also contain the following excipients: ammonium phosphate-monobasic, cellulose-microcrystalline, lactose monohydrate, magnesium stearate, brilliant blue FCF (30mg & 40mg only), quinoline yellow (40mg only), sunset yellow FCF (40mg only).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Isordil Sublingual Tablets, 5 mg Store below 30°C.

Isordil Oral Tablets 10, 30 & 40mg: Store below 25 °C.

6.5 NATURE AND CONTENTS OF CONTAINER

Isordil Sublingual Tablets 5 mg: 20s* and 100s in bottles

Isordil Oral Tablets10 mg, 30 mg and 40 mg : 20s and 100's in bottles* and blister packs*

* Currently not marketed

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

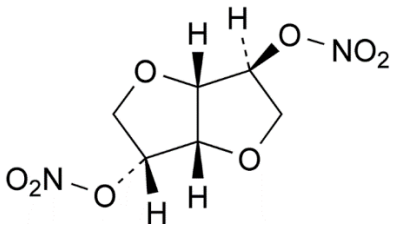
6.7 PHYSICOCHEMICAL PROPERTIES

Isosorbide dinitrate is fine, white or almost white, crystalline powder. It is very slightly soluble in water, very soluble in acetone, sparingly soluble in ethanol (96 per cent).

Isosorbide dinitrate; also known as sorbide nitrate. The chemical name for isosorbide dinitrate is 1,4:3,6-dianhydro-2,5-di-O-nitro-D-glucitol.

Chemical structure

Its structural formula is:



$C_6H_8N_2O_8$ Molecular weight: 236.1

CAS number

87-33-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

Isordil Sublingual Tablets, 5 mg – S3 Pharmacist only Medicine

Isordil Oral Tablets, 10 mg – S2 Pharmacy Medicine

Isordil Oral Tablets, 30 mg – S4 Prescription only Medicine

Isordil Oral Tablets, 40 mg– S4 Prescription only Medicine

8 SPONSOR

Arrow Pharma Pty Ltd
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9 DATE OF FIRST APPROVAL

12 June 1992

10 DATE OF REVISION

4 June 2019

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
all	PI reformat