ISOSORBIDE DINITRATE

℞

ISORDIL

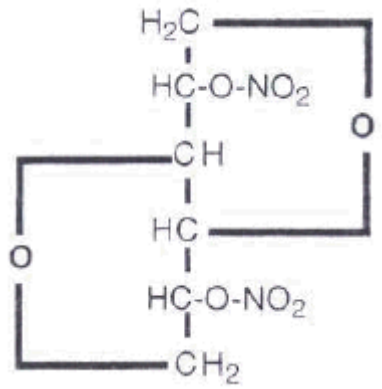
5 mg Sublingual Tablet and 10 mg Oral Tablet

1.0 PHARMACOLOGIC CATEGORY

Organic Nitrate (Vasodilator)

2.0 DESCRIPTION

Isosorbide dinitrate is a white crystalline, odorless compound. It is sparingly soluble in water and freely soluble in alcohol. The chemical name of isosorbide dinitrate is 1, 4: 3, 6-dianhydro-sorbitol-2,5-dinitrate; its chemical structure is



3.0 FORMULATION

Isosorbide dinitrate (Isordil) 10 mg Oral Tablet: Each tablet contains 10 mg Isosorbide dinitrate, USP.
Isosorbide dinitrate (Isordil) 5 mg Sublingual Tablet: Each sublingual tablet contains 5 mg Isosorbide dinitrate, USP.

4.0 CLINICAL PARTICULARS

4.1 Therapeutic Indications

1. Angina Pectoris
    a. Isosorbide dinitrate Oral Tablets:
        i. For prophylaxis of ischemic heart pain associated with coronary insufficiency. Isosorbide dinitrate may reduce the frequency, duration and severity of angina attacks. Exercise tolerance may be improved and the need for nitroglycerin may be reduced. The oral tablets are not indicated for the treatment of an angina attack.
    b. Isosorbide dinitrate Sublingual Tablets:
        i. For treatment of angina pectoris and for prophylaxis in situations likely to provoke an angina attack i.e. physical or emotional stress.

2. Congestive Heart Failure
    a. Acute and chronic congestive heart failure (including that associated with myocardial infarction). Based on current knowledge, isosorbide dinitrate should be considered only as an adjunct to the more conventional modes of therapy (cardiac glycosides and diuretics); however, in refractory cases, it may be used alone or concomitantly with other vasodilators. Isosorbide dinitrate is particularly effective in patients with increased left ventricular end diastolic pressure (LVEDP) – "backward failure" – and normal or approximately normal cardiac output in whom pulmonary congestion or edema is the primary problem. Isosorbide dinitrate is especially recommended when coronary artery disease is the cause of congestive heart failure, in which case its anti-anginal effect of additional value.

4.2 Dosage and Method of Administration

The initial dose should not be more than 5 mg since severe hypotensive response occasionally occurs.

Angina Pectoris

Sublingual Tablets: (Tablets dissolve within 20 seconds) 5 mg to 10 mg sublingually every 2 to 3 hours for the prophylaxis of acute angina; this may be supplemented by a dose of 5 mg to 10 mg prior to stressful situations likely to provoke an attack of angina.

Oral tablets: 5 mg to 30 mg orally 4 times daily, preferably on an empty stomach.

Congestive Heart Failure

In acute and chronic heart failure, both sublingual and oral forms may be used. The selection of sublingual or oral isosorbide dinitrate should be made on the basis of duration of action rather than the magnitude of response, since this is the major difference observed for these dosage forms.

In order to obtain full therapeutic effect, it is important that the dosage of sublingual and oral forms be individualized in accordance with each patient's needs, clinical response and hemodynamic monitoring.

Isosorbide dinitrate therapy should begin with the lowest effective dose and further adjusted as necessary, based on the left ventricular performance. The initial dose really depends on the assessment of how severe the heart failure is. For the treatment of acute congestive heart failure, the rapidly acting sublingual form of isosorbide dinitrate is preferred and should first be administered to stabilize the patient's symptoms or determine the magnitude of hemodynamic response; then it should be followed by the oral form for maintenance therapy.

The average recommended doses for acute and chronic congestive heart failure are the following:

Acute Congestive Heart Failure

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

Oral Tablet: 10 to 40 mg four times daily or as needed

Chronic Congestive Heart 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

Hypersensitivity or idiosyncrasy to isosorbide dinitrate or related compounds.

Do not use isosorbide dinitrate in patients who are taking a soluble guanylate cyclase (GC) stimulator, such as riociguat. Concomitant use may potentiate the hypotensive effects of GC stimulators

4.4 Special Warnings and Precautions for Use

As with other vasodilators, isosorbide dinitrate may cause paradoxical side effects in sensitive patients, which may increase ischemia and may even lead to extension of myocardial damage and advanced congestive heart failure. If one elects to use organic nitrates in the early infarction, hemodynamic monitoring and frequent clinical assessment should be used because of the potential deleterious effects of hypotension. Sildenafil may amplify the vasodilatory effects of nitrates such as Isordil and can result in severe hypotension. Appropriate supportive care has not been studied, but it seems reasonable to treat this as a nitrate overdose.

Severe hypotensive response, particularly with upright posture, may occur with even small doses of isosorbide dinitrate. Paradoxical bradycardia and increased angina pectoris may accompany nitrate-induced hypotension. The drug should be used with caution in subjects who may have blood volume depletion from diuretic therapy or in subjects who have low systolic blood pressure (e.g. below 90 mmg Hg).

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. The importance of tolerance to the appropriate use of isosorbide dinitrate in the management of patients with angina pectoris has not been determined.

In clinical trials in angina patients, there are reports of angina attacks being more easily provoked and of rebound in the hemodynamic effects soon after nitrate withdrawal. It seems prudent therefore, to gradually withdraw patients from isosorbide dinitrate when therapy is being terminated, rather than stopping the drug abruptly.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No long-term studies in animals have been performed to evaluate the carcinogenic potential of this drug. A modified two-litter reproduction study

in rats fed isosorbide dinitrate at 25 or 100 mg/kg/day did not reveal any effects on fertility or gestation or any remarkable growth pathology in any parent or offspring fed isososrbide dinitrate as compared with rats fed a basal–controlled diet.

Use in Children
The safety and effectiveness of isosorbide dinitrate in children has not been established.

Geriatric Use
Clinical studies of isosorbide dinitrate Sublingual and Oral Tablets did not include sufficient number of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in response between the elderly and younger patients.

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.

4.5 Interactions with Other Medicinal Products and Other Forms of Interaction

Nitrates may cause hypotension as a result of peripheral vasodilation. Alcohol may enhance this effect. Patients who are prescribed isosorbide dinitrate should be cautioned accordingly.
Patients receiving antihypertensive drugs, beta adrenergic blockers, or phenothiazines with nitrates should be observed for possible additive hypotensive effects.
Sildenafil – **See section 4.4 Special Warnings and Precautions for Use.**
Riociguat – **See section 4.3 Contraindications**

4.6 Pregnancy and Lactation

Use during Pregnancy
Isosorbide dinitrate has been shown to cause a dose-related increase in embryotoxicity (increase in mummified pups) in rabbits at oral doses 35 and 150 times the maximum recommended human daily dose. There are no adequate and well-controlled studies in pregnant women. Isosorbide dinitrate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use during Lactation
It is not known if isosorbide dinitrate is excreted in breast milk. Because many drugs are excreted in breast milk, a decision should be made whether to discontinue nursing or to discontinue isosorbide dintrate, taking into account the importance of the drug to the mother and the potential risk to the fetus.

4.7 Effects on Ability to Drive and Use Machines

(See section **4.4 Special Warnings and Precautions for Use**)

4.8 Undesirable Effects

1. Cutaneous vasodilation with flushing may occur.
2. Vascular headache is common and may be severe and persistent. Headache is usually relieved by the use of suitable analgesics, or by a temporary reduction in dosage, and tends to disappear after the first week or two of use.
3. Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop. Occasional individuals may exhibit marked sensitivity to the hypotensive effects of nitrates, even with the usual therapeutic dosage. Severe responses such as nausea, vomiting, weakness, restlessness, pallor, perspiration, and collapse can be manifested. Alcohol may intensify this effect. Measures which facilitate venous return (e.g. head-low or Trendelenburg position, deep breathing movement of extremities) will usually reverse the syndrome.
4. Drug rash and/or exfoliative dermatitis may occasionally occur
5. Nausea and vomiting appear to be uncommon

4.9 Overdose

Symptoms of nitrate overdosage may include the following: a prompt fall in blood pressure, persistent and throbbing headache, vertigo, palpitation, visual disturbances, flushed and perspiring skin (later becoming cold and cyanotic), nausea, and vomiting (possibly with colic and even bloody diarrhea), syncope (especially in the upright position), methemoglobinemia with cyanosis and anoxia, initial hyperpnea, dyspnea and slow breathing, slow pulse (dicrotic and intermittent), heart block, increased intracranial pressure with cerebral symptoms of confusion and moderate fever, paralysis and coma followed by clonic convulsions and possibly death due to circulatory collapse.

It is not known what dose of the drug is associated with symptoms of overdosing or what dose of the drug would be life-threatening. The acute oral LD_{50} of isosorbide dinitrate in rats was found to be approximately 1100 mg/kg of body weight. These animal experiments indicate that approximately 500 times the usual therapeutic dose would be required to produce such toxic symptoms in humans. It is not known whether the drug is dialyzable.

Suggested treatment of overdosage: Prompt removal of the ingested material by gastric lavage, if ingestion was recent and the patient is conscious. Keep the patient recumbent in a shock position and comfortably warm. Passive movements of the extremities may aid venous return. Administer oxygen and artificial respiration if necessary. If methemoglobinemia is present, administer methylene blue (1% solution), 1 to 2 mg/kg intravenously. Epinephrine is ineffective in reversing the severe hypotensive events associated with overdose. Epinephrine and related compounds are contraindicated in this situation.

5.0 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Animal Pharmacology

Isosorbide dinitrate, a direct-acting vasodilator, relaxes vascular smooth muscle. When administered intravenously to dogs, isosorbide dinitrate decreases systolic and diastolic blood pressure. Hind limb vascular resistance is decreased after femoral artery injection. Coronary blood flow increases secondary to vasodilation in the isolated rabbit heart. The parent drug was found to be a more potent vasodilator than its mononitrate metabolites.

Clinical Pharmacology

The exact mechanism of action of the nitrates in the relief of angina pectoris is not fully understood. They appear to relieve classic angina pectoris by reducing myocardial oxygen demand, i.e. by decreasing heart's "afterload" and "preload" through dilatation of peripheral venous capacitance and, to a lesser extent, arteriolar resistance vessels. Nitrates may cause a redistribution of coronary blood flow to ischemic areas by selectively dilating large coronary vessels or collateral vessels which may develop secondary to myocardial ischemia.

After therapeutic doses of the drug, systemic arterial pressure is usually decreased; heart rate is unchanged or undergoes slight compensatory increase. In the absence of heart failure, cardiac output transiently increases and then decreases. Pulmonary vascular resistance and pulmonary pressure are decreased.

The anti-anginal effects of isosorbide dinitrate generally occur within 2-5 minutes after administration and last 1-2 hours. The hemodynamic effects of oral tablets are observed from 20-60 minutes and last for 4-6 hours.

5.2 Pharmacokinetic Properties

Gastrointestinal absorption of isosorbide dinitrate is rapid and complete. The drug undergoes an extensive first-pass effect with some interindividual variation. Isosorbide dinitrate is metabolized to two mononitrates which subsequently undergo glucoronidation. Less than 1% of isosorbide dinitrate is bound to plasma proteins. Plasma concentrations of isosorbide dinitrate and mononitrates were compared after administration of sublingual (2x5 mg) and oral (2x10 mg) tablets to volunteers. The sublingual dosage form was more rapidly absorbed than the oral formulation, as evidenced by earlier peak concentrations of the parent drug and the mononitrates. The half-life of the parent drug was 0.2-0.5 hours for the sublingual and oral tablets, respectively. For 2-isosorbide mononitrate, the half life was 2.0 hours for both dosage forms. For 5-isosorbide mononitrate, the half-life of the sublingual tablets was 5.8 hours while that of the oral tablets was 4.5 hours. With chronic administration, significant plasma accumulation of the parent compound occurs, presumably the result of the saturation of the intrahepatic biotransformation process.

The elimination phase after both acute and chronic administration of isosorbide dinitrate appears to be biexponential. Essentially all of the drug is eliminated by the kidneys, principally as isosorbide glucuronide.

6.0 PHARMACEUTICAL PARTICULARS

6.1 Shelf-Life

Please see outer package for the expiry date of the product

6.2 Special Precautions for Storage

Store at temperatures not exceeding 30 °C.

Protect from light. Keep tightly closed and dispense in a tight container.

6.3 Availability

Isordil 5 mg Sublingual Tablets are pink, flat, beveled-edge tablet, debossed with "WYETH" on one side, plain on the other. Available in HPDE bottle of 100's.

Isordil 10 mg Tablets are round, white, biconvex, half-scored compressed tablet debossed with "WYETH" on the other. Available in white plastic bottle of 100's.

7.0 FDA REGISTRATION NUMBER:

5 mg Sublingual Tablet : DRP-6918
10 mg Oral Tablet : DR-XY6511

8.0 DATE OF FIRST AUTHORIZATION / RENEWAL OF AUTHORIZATION:

5 mg Sublingual Tablet : 13 March 2013
10 mg Oral Tablet : 27 October 2011

Keep out of reach of children

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

Seek medical attention immediately at the first sign of any adverse drug reaction.

CAUTION: Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

Manufactured by:
Interphil Laboratories,
Canlubang Industrial Estate
Bo. Pittland, Cabuyao
Laguna Philippines

Marketing Authorization Holder:
Pfizer, Inc.
19F–20F, 8 Rockwell Building,
Hidalgo Drive, Rockwell Center, Poblacion,
Makati City 1210 Metro Manila,
Philippines

Under the Authority of PFIZER, INC. New York, N.Y., U.S.A.

Revision No.: 2.4 Revision Date: 03 March 2022 Reference Document: Admin changes-MAH address update Reference Date: 19 November 2020