PRODUCT MONOGRAPH

ISDN

Isosorbide Dinitrate Tablets USP

5, 10 and 30 mg

Coronary Vasodilator

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THERAPEUTIC CLASSIFICATION

Coronary Vasodilator

ACTIONS AND CLINICAL PHARMACOLOGY

The basic action of isosorbide dinitrate is the relaxation of smooth muscle. Relaxation of peripheral vascular smooth muscle and pooling results in the reduction of preload and afterload on the left ventricle. The effect of the long acting nitrate appears to be mainly peripheral. Although isosorbide dinitrate dilates the coronary arteries there is no incontrovertible evidence that it relieves ischemic heart pain by increasing coronary blood flow.

When administered sublingually, isosorbide dinitrate has an onset of action of 2 to 5 minutes and lasts 1 to 2 hours. After oral administration, relief of angina pectoris begins in 30 minutes and lasts 4 to 6 hours.

Isosorbide dinitrate is metabolized to 2-isosorbide mononitrate and 5-isosorbide mononitrate. After a single oral dose, 80 to 100% of the amount absorbed is excreted in the urine within 24 hours, chiefly as metabolites.

INDICATIONS AND CLINICAL USE

ISDN (isosorbide dinitrate) is indicated for the prophylaxis of ischemic heart pain

associated with coronary insufficiency. Isosorbide dinitrate may reduce the number, duration and severity of anginal attacks, exercise tolerance may be increased and nitroglycerin requirements curtailed.

CONTRAINDICATIONS

Although isosorbide dinitrate may be used for the control of angina pectoris occurring after myocardial infarction, it is suggested that treatment be withheld in the presence of cardiogenic shock, or if there is a risk of shock developing.

Hypersensitivity to isosorbide dinitrate.

Concomitant use of ISDN (isosorbide dinitrate) either regularly and/or intermittently, with VIAGRA® (sildenafil citrate), is absolutely contraindicated.

WARNINGS

Data supporting the use of nitrates during the early days of the acute phase of myocardial infarction, (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

PRECAUTIONS

Use isosorbide dinitrate with caution in patients with glaucoma. Isosorbide dinitrate is a potent vasodilator and causes a slight decrease in mean blood pressure (approximately 10-15 mm Hg) in some patients when used in therapeutic doses. Caution should be exercised in using the drug in patients who are prone to, or might be affected by, hypotension. In patients with renal

insufficiency, isosorbide dinitrate should be used with caution since the hypotensive effect may cause a dangerous reduction in renal blood flow.

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

Drug Interaction

Concomitant use of ISDN (isosorbide dinitrate) and VIAGRA® (sildenafil citrate) can potentiate the hypotensive effect of ISDN (isosorbide dinitrate). This could result in life-threatening hypotension with syncope or myocardial infarction and death. Therefore, VIAGRA® (sildenafil citrate) should not be given to patients receiving ISDN (isosorbide dinitrate) therapy.

ADVERSE REACTIONS

As with nitroglycerin and other nitrates, vascular headache occurs and it may be severe and persistent. This adverse effect occurs most frequently at the beginning of therapy. Headache usually can be controlled by temporary dosage reduction, concomitant administration of suitable analgesics or by administering the drug during meals. These headaches usually disappear within 1 week of continuous, uninterrupted therapy. It is usually best to advise the patient of their possible occurrence and of their importance in regard to the prevention of angina. Drug and/or exfoliative dermatitis occasionally occur. Signs of cerebral ischemia associated with postural hypotension such as weakness, transient episodes of dizziness may occasionally develop. Cutaneous vasodilatation with flushing may occur. Rarely a marked sensitivity to the hypotensive effects of the drug and severe response (nausea, vomiting, restlessness,

perspiration and collapse) can occur and alcohol may enhance this effect. Isosorbide dinitrate can antagonize the effects of histamine or epinephrine, acetylcholine and similar agents.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms

Related to vasodilatation; cutaneous flushing, headache, nausea, dizziness and hypotension.

Treatment

Gastric lavage. Symptomatic and supportive therapy should include ventilation with oxygen and vasopressor amines if indicated (norepinephrine is suitable).

DOSAGE AND ADMINISTRATION

Sublingual Tablets (tablets dissolve in 20 seconds in the mouth)

5 to 10 mg sublingually, every 2 to 4 hours for the prophylaxis of acute angina; may be supplemented by a dose of 5 to 10 mg sublingually prior to stressful situations likely to provoke an attack of angina.

Oral Titradose Tablets

5 to 30 mg orally 4 times daily, according to therapeutic and patient response.

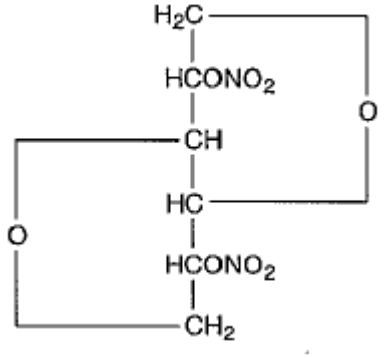
PHARMACEUTICAL INFORMATION

Drug Substance

Proper/Common Name: isosorbide dinitrate

Chemical Name: D-Glucital, 1,4:3,6-dianhydro-, dinitrate

Structural Formula:



Molecular Formula: $C_6H_8N_2O_8$

Molecular Weight: 236.14

Description: Isosorbide dinitrate is a white, crystalline odourless compound. It is sparingly soluble in water, and is freely soluble in acetone, ether, and alcohol. It has a melting point of 70°C and optical rotation of $^{+}134$ (c=1.0, alcohol, 20°C).

Composition

In addition to the active ingredient isosorbide dinitrate, each tablet contains the non-medicinal ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium,

magnesium stearate, colloidal silicon dioxide (5 mg and 30 mg tablets only), and D&C Red #30 AL Lake (5 mg tablets only).

Stability and Storage Recommendations

Store at room temperature 15-30°C. Protect from moisture.

AVAILABILITY OF DOSAGE FORMS

ISDN 5 mg Sublingual: Each pink, round, flat-faced sublingual tablet engraved '5' on one side, contains 5 mg of isosorbide dinitrate. Available in bottles of 100 and 500.

ISDN 10 mg Oral: Each white, round, flat-faced, scored tablet engraved '10' on one side, contains 10 mg of isosorbide dinitrate. Available in bottles of 100 and 1000, unit dose packages of 100 (10x10s).

ISDN 30 mg Oral: Each white, round, flat-faced, scored tablet engraved '30' on one side, contains 30 mg of isosorbide dinitrate. Available in bottles of 100 and 1000, unit dose packages of 100 (10x10s).

PHARMACOLOGY

Isosorbide dinitrate (ISDN) dilates vascular smooth muscle throughout the body. ISDN exerts its strongest effect on the venous system and a lesser effect on the arterial circulation.

Mason et al., studied the peripheral circulatory actions of nitroglycerin in normal human volunteers. Mean arterial pressure declined slightly, forearm blood flow increased, the calculated forearm vascular resistance decreased by a mean of 35% and venous tone declined by an average of 19%. The changes in all four variables were statistically significant.

Goffredo et al. measured the changes in coronary vascular diameter of dogs following the administrations of 1 mg ISDN intracutaneously, 2 mg ISDN intravenously, 40 mg ISDN orally in the form of crushed tablets, and 40 mg ISDN in the form of intact tablets. The intracutaneous and intravenous administration of the drug produced a mean coronary vasodilation of 7%, the effects of the intravenous administration dissipating somewhat faster than those following the intracutaneous administration. Vasodilation was also clearly measurable after the oral administrations of the drug, although the effects were more pronounced with the crushed tablets.

As with other nitrates, the precise mechanism of action of ISDN on the smooth muscle cells of blood vessels has not been determined. It appears that ISDN and related compound acts on the specific nitrate receptor site in the vascular wall and react with sulfhydryl group producing a nitrite ion which is a generalized smooth muscle relaxant.

Needleman et al. showed that incubating rabbit aortic strips with glyceryl trinitate at alkaline pH resulted in the formation of nitrite ions and a net loss of titratable sulfhydryl. A direct relationship between tissue contractibility and sulfhydryl groups present was also demonstrated.

Nitrate tolerance was induced in vitro by incubating aortal strips with glyceryl trinitrate. This tolerance was reversible by disulfide reducing agents, demonstrating that the oxidation of the

sulfhydryl receptor site is the cause of the reduced effectiveness of the nitrates. The same results were obtained when tolerance was developed in vivo in rats (100 mg/kg t.i.d., 3 days). Thoracic aortas from the nitrate-tolerant animals showed an approximately 500-fold shift in vitro glyceryl trinitrate sensitivity, but could be returned to near normal sensitivity by treatment with dithiothreitol.

After oral administration ISDN appears to be rapidly absorbed. Equilibrium dialysis experiments suggest that ISDN is not extensively bound to plasma proteins. According to a recent study, the disposition of ISDN showed a clear bi-exponential characteristic with half lives of approximately 1.5 and 4 hours for the alpha and beta phases, respectively. According to this study, plasma ISDN concentrations after chronic dosing were in general higher than those obtained after the comparable single doses.

When administered sublingually, ISDN absorbs rapidly and essentially completely. Recent studies show that elimination follows 1st order kinetics (1 compartment model) with the half life of about 30 minutes.

Nitrates are rapidly metabolized in the liver by glutathion reductase. Recent investigations indicate that there is a wide interindividual variation in the pharmacokinetics of ISDN and that some of the metabolites are also active. Two- and 5-isosorbide mononitrate were found to exert a lesser but longer lasting hemodynamic effect than ISDN.

Thus, the active metabolites may contribute to the duration of action of ISDN. Elimination occurs via the urine and is practically 100% within 24 hours post-administration. Intact ISDN is not found in urine. Twenty to 30% of the dose is excreted as 5-ISMN, 2-ISMN, isosorbide and

isoiodide. The remainder is excreted primarily as the ether glucuronide of 5-ISMN and isosorbide.

TOXICOLOGY

Following the oral administration of the drug in rats, the acute LD_{50} was found to be approximately 1,100 mg/kg of body weight.

Chronic oral toxicity was determined in rats and dogs. The following dosage levels were employed in the chronic toxicity studies:

Rats: 100 mg/kg, 50 mg/kg, 25 mg/kg, and control.
Dogs: 100 mg/kg, 50 mg/kg, 25 mg/kg, and control.

Male rats and dogs at the highest dosage level showed a decrease in growth curve as compared to control animals and animals in the lower dosage groups. Histological examination of the tissues did not reveal evidence to toxic injury. There was no evidence of an effect on bone marrow, or the hematopoietic system, nor the peripheral blood. Examination of blood samples in dogs for the presence of methemoglobin failed to reveal a significant level of the pigment.

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