ISOSORBIDE MONONITRATE

VASOTRATE-60 OD

60 mg Sustained Release Tablet

Anti-Angina

xxxxxxxx-5343

FORMULATION

Each sustained release tablet contains:

Isosorbide mononitrate ..... 60 mg

PRODUCT DESCRIPTION

Isosorbide Mononitrate (Vasotrate-60 OD) 60 mg Sustained Release Tablet is a light yellow coloured round biconvex, film coated tablet with break line on one side.

CLINICAL PHARMACOLOGY

Mechanism of Action

The isosorbide mononitrate, the major active metabolite of isosorbide dinitrate; most of the clinical activity of the dinitrate is attributable to the mononitrate.

The principal pharmacological action of isosorbide mononitrate and all organic nitrates in general is relaxation of vascular smooth muscle, producing dilatation of peripheral arteries and veins, especially the latter. Dilatation of the veins promotes peripheral pooling of blood, decreases venous return to the heart, thereby reducing left ventricular end-diastolic pressure and pulmonary capillary wedge pressure (preload). Arteriolar relaxation reduces systemic vascular resistance, systolic arterial pressure and mean arterial pressure (afterload). Dilatation of the coronary arteries also occurs. The relative importance of preload reduction, afterload reduction, and coronary dilatation remains undefined.

Pharmacodynamics

Dosing regimens for most chronically used drugs are designed to provide plasma concentrations that are continuously greater than a minimally effective concentration. This strategy is inappropriate for organic nitrates. Several well-controlled clinical trials have used exercise testing to assess the antianginal efficacy of continuously delivered nitrates. In the large majority of these trials, active agents were indistinguishable from placebo after 24 hours (or less) of continuous therapy. Attempts to overcome tolerance by dose escalation, even to doses far in excess of those used acutely, have consistently failed. Only after nitrates have been absent from the body for several hours has their antianginal efficacy been restored. Isosorbide mononitrate extended-release tablets, during long-term use over 42 days dosed at 120 mg once daily, continued to improve exercise performance at 4 hours and at 12 hours after dosing but its effects (although better than placebo) are less than or at best equal to the effects of the first dose of 60 mg.

Pharmacokinetics

After oral administration of isosorbide mononitrate as a solution or immediate-release tablets, maximum plasma concentrations of isosorbide mononitrate are achieved in 30 to 60 minutes, with an absolute bioavailability of approximately 100%. After intravenous administration, isosorbide mononitrate is distributed into total body water in about 9 minutes with a volume of distribution of approximately 0.6-0.7 L/kg. Isosorbide mononitrate is approximately 5% bound to human plasma proteins and is distributed into blood cells and saliva.

Isosorbide mononitrate is primarily metabolized by the liver, but unlike oral isosorbide dinitrate, it is not subject to first-pass metabolism. Isosorbide mononitrate is cleared by denitration to isosorbide and glucuronidation as the mononitrate, with 96% of the administered dose excreted in the urine within 5 days and only about 1% eliminated in the feces. At least six different compounds have been detected in urine, with about 2% of the dose excreted as the unchanged drug and at least five metabolites. The metabolites are not pharmacologically active. Renal clearance accounts for only about 4% of total body clearance. The mean plasma elimination half-life of isosorbide mononitrate is approximately 5 hours.

INDICATION

Used in the prophylaxis of angina and as adjunct in congestive heart failure.

DOSAGE AND ADMINISTRATION

The recommended starting dose is 30 mg (given as a single 30 mg tablet or as 1/2 of a 60 mg tablet) or 60 mg (given as a single tablet) once daily. After several days, the dosage may be increased to 120 mg (given as a single 120 mg tablet or as two 60 mg tablets) once daily. Rarely, 240 mg may be required. It should be taken in the morning on arising, or as prescribed by the physician.

isosorbide Mononitrate sustained release should not be chewed or crushed and should be swallowed together with a half-glassful of fluid.

CONTRAINDICATION

Isosorbide mononitrate are contraindicated in patients who have shown hypersensitivity or idiosyncratic reactions to other nitrates or nitrites.

WARNINGS AND PRECAUTIONS

Amplification of the vasodilatory effects of isosorbide mononitrate by sildenafil can result in severe hypotension. The time course and dose dependence of this interaction have not been studied. Appropriate supportive care has not been studied, but it seems reasonable to treat this as a nitrate overdose, with elevation of the extremities and with central volume expansion. Severe hypotension, particularly with upright posture, may occur with even small doses of isosorbide mononitrate. This drug should, therefore, be used with caution in patients who may be volume depleted or who, for whatever reason, are already hypotensive. Hypotension induced by isosorbide mononitrate may be accompanied by paradoxical bradycardia and increased angina pectoris.

The benefits of isosorbide mononitrate in patients with acute myocardial infarction or congestive heart failure have not been established; because the effects of isosorbide mononitrate are difficult to terminate rapidly, this drug is not recommended in these settings.

If isosorbide mononitrate is used in these conditions, careful clinical or hemodynamic monitoring must be used to avoid the hazards of hypotension and tachycardia.

It should not be used in patients with hypovolemia, marked anemia, heart failure due to obstruction (including constrictive pericarditis), or raised intracranial pressure due to head trauma or cerebral hemorrhage. It should be used with caution in patients with severe renal or severe hepatic impairment, hypothyroidism, malnutrition, or hypothermia.

Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy. In industrial workers who have had long-term exposure to unknown (presumably high) doses of organic nitrates, tolerance clearly occurs. Chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitrates from these workers, demonstrating the existence of true physical dependence. The importance of these observations to the routine, clinical use of oral isosorbide mononitrate is not known.

As with other nitrates, daily headaches sometimes accompany treatment with isosorbide mononitrate. In patients who get these headaches, the headaches are a marker of the activity of the drug. Patients should resist the temptation to avoid headaches by altering the schedule of their treatment with isosorbide mononitrate, since loss of headache may be associated with simultaneous loss of antianginal efficacy. Aspirin or acetaminophen often successfully relieves isosorbide mononitrate-induced headaches with no deleterious effect on isosorbide mononitrate's antianginal efficacy.

Treatment with isosorbide mononitrate may be associated with lightheadedness on standing, especially just after rising from a recumbent or seated position. This effect may be more frequent in patients who have also consumed alcohol.

PREGNANCY AND LACTATION

Pregnancy Category B. In studies designed to detect effects of isosorbide mononitrate on embryo-fetal development, doses of up to 240 or 248 mg/kg/day, administered to pregnant rats and rabbits, were unassociated with evidence of such effects. These animal doses are about 100 times the maximum recommended human dose (120 mg in a 50 kg woman) when comparison is based on body weight; when comparison is based on body surface area, the rat dose is about 17 times the human dose and the rabbit dose is about 38 times the human dose. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, isosorbide mononitrate extended-release tablets should be used during pregnancy only if clearly needed.

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when isosorbide mononitrate is administered to a nursing mother.

DRUG INTERACTIONS

The vasodilating effects of isosorbide mononitrate may be additive with those of other vasodilators and other drugs with hypotensive actions. Alcohol, in particular, has been found to exhibit additive effects of this variety. Marked symptomatic orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustments of either class of agents may be necessary.

ADVERSE EFFECTS

Isosorbide mononitrate may cause flushing of the face, dizziness, tachycardia, throbbing headache. Large doses may cause vomiting, restlessness, blurred vision, hypotension (which can be severe), syncope, and rarely cyanosis, and methahemoglobinemia, impairment of respiration and bradycardia may ensue.

"For suspected adverse drug reaction, report to FDA: www.fda.gov.ph or to TORRENT: www.torrentpharma.com".

Patient to seek medical attention immediately at the first sign of any adverse drug reaction shall appear.

OVERDOSAGE AND TREATMENT

Hemodynamic Effects

The ill effects of isosorbide mononitrate overdose are generally the result of isosorbide mononitrate's capacity to induce vasodilatation, venous pooling, reduced cardiac output, and hypotension. These hemodynamic changes may have protean manifestations, including increased intracranial pressure, with any or all of persistent throbbing headache, confusion, and moderate fever; vertigo, palpitations; visual disturbances; nausea and vomiting (possibly with colic and even bloody diarrhea); syncope (especially in the upright posture); air hunger and dyspnea, later followed by reduced ventilatory effort; diaphoresis, with the skin either flushed or cold and clammy; heart block and bradycardia; paralysis; coma; seizures and death.

Laboratory determinations of serum levels of isosorbide mononitrate and its metabolites are not widely available, and such determinations have, in any event, no established role in the management of isosorbide mononitrate overdose.

There are no data suggesting what dose of isosorbide mononitrate is likely to be life threatening in humans. In rats and mice, there is significant lethality at doses of 2000 mg/kg and 3000 mg/kg, respectively.

No data are available to suggest physiological maneuvers (e.g., maneuvers to change the pH of the urine) that might accelerate elimination of isosorbide mononitrate. In particular, dialysis is known to be ineffective in removing isosorbide mononitrate from the body.

No specific antagonist to the vasodilator effects of isosorbide mononitrate is known, and no intervention has been subject to controlled study as a therapy of isosorbide mononitrate overdose. Because the hypotension associated with isosorbide mononitrate overdose is the result of venodilatation and arterial hypovolemia, prudent therapy in this situation should be directed toward an increase in central fluid volume. Passive elevation of the patient's legs may be sufficient, but intravenous infusion of normal saline or similar fluid may also be necessary.

The use of epinephrine or other arterial vasoconstrictors in this setting is likely to do more harm than good. In patients with renal disease or congestive heart failure, therapy resulting in central volume expansion is not without hazard. Treatment of isosorbide mononitrate overdose in these patients may be subtle and difficult, and invasive monitoring may be required.

Methemoglobinemia

Methemoglobinemia has been reported in patients receiving other organic nitrates, and it probably could also occur as a side effect of isosorbide mononitrate. Certainly nitrate ions liberated during metabolism of isosorbide mononitrate can oxidize hemoglobin into methemoglobin. Even in patients totally without cytochrome b reductase activity, however, and even assuming that the nitrate moiety of isosorbide mononitrate is quantitatively applied to oxidation of hemoglobin, about 2 mg/kg of isosorbide mononitrate should be required before any of these patients manifest clinically significant (≥10%) methemoglobinemia. In patients with normal reductase function, significant production of methemoglobin should require even larger doses of isosorbide mononitrate. In one study in which 36 patients received 2-4 weeks of continuous nitroglycerin therapy at 3.1 to 4.4 mg/hr (equivalent, in total administered dose of nitrate ions, to 7.8 to 11.1 mg of isosorbide mononitrate per hour), the average methemoglobin level measured was 0.2%; this was comparable to that observed in parallel patients who received placebo.

Notwithstanding these observations, there are case reports of significant methemoglobinemia in association with moderate overdoses of organic nitrates. None of the affected patients had been thought to be unusually susceptible.

Methemoglobin levels are available from most clinical laboratories. The diagnosis should be suspected in patients who exhibit signs of impaired oxygen delivery despite adequate cardiac output and adequate arterial pO2. Classically, methemoglobinemic blood is described as chocolate brown without color change on exposure to air. When methemoglobinemia is diagnosed, the treatment of choice is methylene blue, 1 to 2 mg/kg intravenously.

STORAGE AND CONDITION

Store at temperatures not exceeding 30°C.

CAUTION

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

AVAILABILITY

Isosorbide Mononitrate (Vasotrate-60 OD) 60 mg Sustained Release Tablet - PVC-Alu Blister Pack of 7's (Box of 70's) - DRP-2701

DATE OF FIRST AUTHORIZATION

December 26, 2007

DATE OF REVISION

September 2016

torrent PHARMA

Manufactured by :
TORRENT PHARMACEUTICALS LTD.
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Imported and Distributed by :
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Makati City, PHILIPPINES

PRODUCT NAME :	VASOTRATE 60 OD	**COUNTRY :** Philippines	**LOCATION :** Chhatral		**Supersedes A/W No.:**		
ITEM / PACK :	Insert	**NO. OF COLORS:** 1	**REMARK :**				
DESIGN STYLE :	Front	**PANTONE SHADE NOS.:**	**SUBSTRATE :**				
CODE :	xxxxxxxxxx-5343	Black	**Activities**	**Department**	**Name**	**Signature**	**Date**
DIMENSIONS (MM) :	150 x 220		Prepared By	**Pkg.Dev**			
ART WORK SIZE :	S/S		Reviewed By	**Pkg.Dev**			
DATE :	02-12-2017		Approved By	**Quality**			