For the use of a Registered Medical Practitioner or Hospital or a Laboratory only

VASOTRATE 30 & 60 OD
(Isosorbide mononitrate Sustained Release Tablets 30 mg, 60mg)

COMPOSITION
VASOTRATE-30 OD
Each film coated sustained release tablet contains:
Diluted Isosorbide Mononitrate I.P. equivalent to
Isosorbide Mononitrate 30mg
Colour: Titanium Dioxide I.P.

VASOTRATE-60 OD
Each film coated sustained release tablet contains:
Diluted Isosorbide mononitrate I.P. equivalent to
Isosorbide mononitrate 60mg
Colour: Yellow oxide of Iron and Titanium Dioxide I.P

DOSAGE FORM
Sustained release tablet.

INDICATIONS
For prophylaxis of angina pectoris due to coronary artery disease.

POSOLOGY AND METHOD OF ADMINISTRATION
For oral administration.
Adults

The recommended starting dose of VASOTRATE OD Tablets 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. The daily dose of Vasotrate Tablets should be taken in the morning on arising. Vasotrate Sustained release Tablets should not be chewed or crushed and should be swallowed together with a half-glassful of fluid. Do not break the 30 mg tablet.

Elderly
There are no indications that adjustment is necessary.

Children
There are as yet no data on the safety and efficacy of isosorbide mononitrate in children.

CONTRAINDICATIONS
Hypersensitivity to isosorbide mononitrate or to any of the excipients.
Acute myocardial infarction with low filling pressures, hypertrophic obstructive cardiomyopathy, constrictive pericarditis, cardiac tamponade, aortic/mitral stenosis and severe anaemia, hypovolaemia, conditions causing raised intracranial pressure (e.g. cerebral haemorrhage, head trauma) and closed-angle glaucoma. Severe cerebrovascular insufficiency or hypotension are contraindications to use.

Phosphodiesterase type-5 inhibitors (e.g. sildenafil) have been shown to potentiate the hypotensive effects of nitrates, their co-administration with nitrates or nitric oxide donors is therefore contraindicated.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The lowest effective dose should be used.

There is a risk of tolerance developing to modified release preparations. In such patients intermittent therapy may be more appropriate.

Therapy should not be discontinued suddenly. Both dosage and frequency should be tapered gradually.

Symptoms of circulatory collapse may arise after the first dose, particularly in patients with labile circulation.

Hypotension induced by nitrates may be accompanied by paradoxical bradycardia and increased angina.

Severe postural hypotension with light-headedness and dizziness is frequently observed after the consumption of alcohol.

Vasotrate OD Tablets are not indicated for relief of acute anginal attacks: in the event of an acute attack, glyceryl trinitrate should be used.

The administration of isosorbide mononitrate causes a decrease of) effective renal plasma flow (eRPF) in cirrhotic patients and should be used with caution.

Caution should be used in patients who have a recent history of myocardial infarction and in patients suffering from hypothyroidism, hypothermia, malnutrition, and severe liver or renal disease. Oral nitrates should also be used with caution in patients with angina due to other causes, or pre-existing hyperdynamic conditions.

Since oral nitrates can cause venous dilatation, they should not be used in patients with increased intracranial pressure.

DRUG INTERACTION

The hypotensive effect of nitrates will be increased if used together with phosphodiesterase type-5 inhibitors (e.g. sildenafil). This might lead to life threatening cardiovascular complications.

Any medication which may cause hypotension may have its hypotensive effects potentiated by concurrent administration of Vasotrate Tablets (e.g. alcohol, antihypertensives, vasodilators, calcium channel blockers, and diuretics).

Reports suggest that concomitant administration of isosorbide mononitrate may increase the blood level of dihydroergotamine and its hypertensive effect.

Alcohol can attenuate cerebral ischaemia associated with postural hypotension.

Isosorbide mononitrate can act as a physiological antagonist to noradrenaline, acetylcholine and histamine.

FERTILITY, PREGNANCY AND LACTATION

Pregnancy

The safety and efficacy of Isosorbide mononitrate Tablets during pregnancy in humans has not been established. Animal studies have shown reproductive toxicity. Isosorbide mononitrate should only be used in pregnancy if, in the opinion of the physician, the possible benefits of treatment outweigh the hazards.

Breast-feeding

The safety and efficacy of [2]Isosorbide mononitrate during lactation in humans has not been established. It is not known whether nitrates are excreted in human milk and therefore caution

should be exercised when administered to nursing women. Isosorbide mononitrate should only be used during lactation if, in the opinion of the physician, the possible benefits of treatment outweigh the hazards.
[1] PL 06464/0506-0020; 11/12/2009
[2] PL 06464/0506-0020; 11/12/2009

Effects on ability to drive and use machines
The patient should be warned not to drive or operate machinery if hypotension or dizziness occurs.

UNDESIRABLE EFFECTS
Most of the adverse reactions are pharmacodynamically mediated and dose dependent.
Headache is very common (>10%). The incidence of headache usually disappears after 1-2 weeks of treatment.
Immune system disorders
Allergic dermatitis, exfoliative dermatitis.
Nervous system disorders
Headache, restlessness, somnolence, pituitary haemorrhage.
Cardiac disorders
Tachycardia, bradycardia - these symptoms generally disappear during long-term treatment.
Vascular disorders
Flushing, dizziness, orthostatic hypotension - these symptoms generally disappear during long-term treatment. Pallor. Circulatory collapse (sometimes accompanied by bradyarrhythmia, bradycardia and syncope). Severe hypotension may lead to enhanced angina pectoris symptoms.
Respiratory, thoracic and mediastinal disorders
Hypoxia.
Gastrointestinal disorders
Nausea, vomiting, diarrhoea
Skin and subcutaneous tissue disorders
Hyperhidrosis, pruritus.
Musculoskeletal and connective tissue disorders
Myalgia.
General disorders and administration site conditions
Asthenia.

OVERDOSE
Symptoms and signs
Pulsing headache. More serious symptoms are excitation, flushing, cold perspiration, nausea, vomiting, vertigo, syncope, tachycardia and a fall in blood pressure. A rise in intracranial pressure with confusion and neurological deficits can sometimes occur.
Methaemoglobinaemia (cyanosis, hypoxaemia, change in mental status, respiratory depression, convulsions, cardiac arrhythmias, circulatory failure and raised intracranial pressure) occurs rarely.

Management
Induction of emesis, activated charcoal.
In case of pronounced hypotension the patient should first be placed in the supine position with legs raised. If necessary, fluids should be administrated intravenously.

Consider oral activated charcoal if ingestion of a potentially toxic amount has occurred within 1 hour. Observe for at least 12 hours after the overdose. Monitor blood pressure and pulse.
If methaemoglobinaemia occurs seek expert advice. Treat with supplemental oxygen and methylene blue. In cases not responding to methylene blue or where methylene blue is contraindicated consider exchange transfusion or red blood cell concentrates. In case of cerebral convulsions, consider diazepam or clonazepam IV or, if therapy fails, phenobarbital, phenytoin or propofol anaesthesia.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: organic nitrate
ATC code: C01DA14
Mechanism of action
Organic nitrates (including glyceryl trinitrate, isosorbide dinitrate and isosorbide mononitrate) are potent relaxers of smooth muscle. They have a powerful effect on vascular smooth muscle with less effect on bronchiolar, gastrointestinal, ureteral and uterine smooth muscle. Low concentrations dilate both arteries and veins.
Venous dilatation pools blood in the periphery leading to a decrease in venous return, central blood volume, and ventricular filling volumes and pressures. Cardiac output may remain unchanged or it may decline as a result of the decrease in venous return. Arterial blood pressure usually declines secondary to a decrease in cardiac output or arteriolar vasodilatation, or both. A modest reflex increase in heart rate results from the decrease in arterial blood pressure. Nitrates can dilate epicardial coronary arteries including atherosclerotic stenoses.

Pharmacodynamic effects
The cellular mechanism of nitrate-induced smooth muscle relaxation has become apparent in recent years. Nitrates enter the smooth muscle cell and are cleaved to inorganic nitrate and eventually to nitric oxide. This cleavage requires the presence of sulphydryl groups, which apparently come from the amino acid cysteine. Nitric oxide undergoes further reduction to nitrosothiol by further interaction with sulphydryl groups. Nitrosothiol activates guanylate cyclase in the vascular smooth muscle cells, thereby generating cyclic guanosine monophosphate (cGMP). It is this latter compound, cGMP that produces smooth muscle relaxation by accelerating the release of calcium from these cells.

Pharmacokinetic properties

Absorption
Isosorbide mononitrate is readily absorbed from the gastro-intestinal tract. After oral administration of sustained release tablets, Isosorbide mononitrate is slowly and completely absorbed as compared to Isosorbide dinitrate.

Distribution
Following oral administration of sustained release tablet formulation of Isosorbide mononitrate, peak plasma levels are reached in approximately 3 hours. Isosorbide mononitrate are distributed throughout the whole body fluid. Unlike isosorbide dinitrate, isosorbide mononitrate does not undergo first pass hepatic metabolism and bioavailability is 77-80%.

Elimination
The pharmacokinetics are unaffected by the presence of heart failure, renal or hepatic insufficiency. Isosorbide mononitrate is excreted mainly in the urine; compounds recovered in urine after isosorbide mononitrate administration have included isosorbide, sorbitol, and

conjugates; only 2% of a dose is excreted as unchanged drug. About 96% of an administered dose of isosorbide mononitrate is excreted in urine and about 1% in feces within 5 days; most excretion (about 93%) occurs within 48 hours. An elimination half-life of about 4-5 hours has been reported.

PRECLINICAL SAFETY DATA
[3]High concentrations of isosorbide mononitrate in rats is associated with prolonged gestation and parturition, stillbirths and deaths.

DIRECTION FOR USE
The tablets or divided halves of tablet must be swallowed intact without crushing or chewing.

EXPIRY DATE
Do not use later than the date of expiry.

PACKAGING INFORMATION
VASOTRATE-30, VASOTRATE-60 is available in Blister strip of 7 Tablets.

STORAGE AND HANDLING INSTRUCTIONS
Keep in a dry place at a temperature not exceeding 30°C, Protected from light.
Keep out of reach of children.

MARKETED BY
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