For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only. xxxxxxxx-8883

# VASOTRATE-OD

(Isosorbide Mononitrate Sustained Release Tablets, 30mg & 60mg)

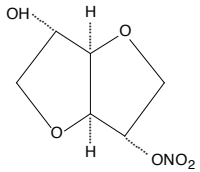
**COMPOSITION**

**Vasotrate 30-OD :** Each film coated sustained release tablet contains Diluted Isosorbide Mononitrate B.P. equivalent to Isosorbide Mononitrate..... 30mg.

**Vasotrate 60-OD :** Each film coated sustained release tablet contains Diluted Isosorbide Mononitrate B.P. equivalent to Isosorbide Mononitrate..... 60mg.

**PROPERTIES**

Vasotrate-OD (Isosorbide mononitrate) is an organic nitrate with vasodilator effects on both arteries and veins. Vasotrate-OD film coated tablets contain 30 & 60 mg of Isosorbide mononitrate in a sustained release formulation. The chemical name for Vasotrate-OD is 1, 4 : 3, 6-dianhydro-,D-glucitol 5-nitrate :




**CLINICAL PHARMACOLOGY**

***PHARMACODYNAMICS***

Vasotrate-OD is an oral sustained release formulation of Isosorbide mononitrate. The principal pharmacological action of Vasotrate-OD is relaxation of vascular smooth muscle, producing dilation of peripheral veins, consequently reducing the preload and also arteries, thereby reducing the afterload. Dilatation of the coronary arteries also occurs.

The standard oral formulation of Isosorbide mononitrate has shown significant antianginal efficacy when administered twice daily in an asymmetric fashion. Despite improvements in treadmill exercise walking times to angina after short-term dosing, an attenuation of these improvements can develop within as short a time as 24 hours and, in some cases, can be almost complete by 7 to 10 days. It has been shown that tolerance to Isosorbide mononitrate can be avoided if the plasma nitrate level is reduced for some hours over the 24h period. ***Vasotrate-OD in a sustained release formulation can, if administered once daily, give reproducible therapeutic plasma concentration during the day, with a gradual fall in nitrate concentrations during the latter part of the 24h period, producing a nitrate-poor rather than a nitrate-free interval. This circumvents the problem of development of tolerance on one hand and prevents rebound phenomenon on the other.***

***PHARMACOKINETICS***

The pharmacokinetics of sustained release formulation of Vasotrate-OD has been investigated in healthy volunteers and in patients with chronic stable angina. Vasotrate-OD is approximately 5% bound to human plasma proteins and is distributed into blood cells and saliva. Maximum plasma concentration ($C_{max}$) and area under the plasma concentration-time curve from 0 to 24 hours ($AUC_{0-24}$) are dose proportional between 30mg and 240mg. Time to reach $C_{max}$ ($t_{max}$) is approximately 3-4 hours. Thereafter, plasma concentrations slowly decline to mean value 24 hours after administration of 60mg, of 109 mg/L. The liver primarily metabolizes Vasotrate-OD, but it is not subjected to first-pass metabolism. Vasotrate-OD 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 Vasotrate-OD is approximately 6 hours. Administration of food delays the absorption of Vasotrate-OD, as indicated by an increase in mean $t_{max}$ from 3.1 to 6.5 hours and an increase in apparent absorption half-life from 2.13 to 3.30 hours in healthy volunteers. However, these increases were associated with a <10% change in $C_{max}$ and AUC. The pharmacokinetic profile of Vasotrate-OD in patients with renal or hepatic impairment or cardiac dysfunction is generally similar to that in healthy volunteers. There are no significant differences in any of the pharmacokinetic variables of Vasotrate-OD between elderly and younger individuals. The pharmacokinetics of Vasotrate-OD are dose proportional.

**INDICATIONS**

Vasotrate-OD tablets are indicated for prevention of angina pectoris due to coronary artery disease.

**CONTRAINDICATIONS**

Vasotrate-OD tablets are contraindicated in patients who have shown hypersensitivity or idiosyncratic reactions to other nitrates or nitrites.

**WARNINGS**

The benefits of Vasotrate-OD in patients with acute myocardial infarction or congestive heart failure have not been established; because the effects of Vasotrate-OD are difficult to terminate rapidly, this drug is not recommended in these settings. If Vasotrate-OD is used in these conditions, careful clinical or hemodynamic monitoring must be used to avoid the hazards of hypotension and tachycardia.



**PRECAUTIONS**

Severe hypotension, particularly with upright posture may occur with even small doses of Vasotrate-OD. This drug should therefore be used with caution in patients who may be volume depleted or hypotensive. Hypotension induced by Vasotrate-OD maybe accompanied by paradoxical bradycardia and increased angina pectoris. 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.

**Information for Patients**

Patients should be told that the antianginal efficacy of Vasotrate-OD tablets could be maintained by carefully following the prescribed schedule of dosing. For most patients, this can be accomplished by taking the dose on arising. As with other nitrates, daily headaches sometimes accompany treatment with Vasotrate-OD. In patients who get these headaches, they are a marker of the activity of the drug.

**Use in Pregnancy and Nursing mothers**

*Teratogenic Effects*

In studies designed to detect effects of Vasotrate-OD 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. Because animal reproduction studies are not always predictive of human response, Vasotrate-OD tablets should be used during pregnancy, only if clearly needed.

*Non-teratogenic Effects*

Neonatal survival and development and incidence of stillbirths were adversely affected when pregnant rats were administered oral doses of 750 mg/kg/day during late gestation and lactation.

*Nursing Mothers*

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 Vasotrate-OD is administered to a nursing mother.

**ADVERSE REACTIONS**

Overall Vasotrate-OD treatment appears to be well tolerated. As with other nitrates, headache is the most frequently reported adverse event. Other adverse events are dizziness, fatigue, nausea, musculoskeletal pain, viral infection and rhinitis.

**DRUG INTERACTIONS**

The vasodilating effects of Vasotrate-OD may be additive with those of other vasodilators. Dose adjustments of either class of agents may be necessary. Alcohol, in particular, has been found to exhibit additive effects of this variety.

**DOSAGE AND ADMINISTRATION**

The recommended starting dose of Vasotrate-OD is 30mg or 60mg once daily. After several days dose may be increased to 120mg once daily. The daily dose of Vasotrate-OD tablets may be taken in the morning on arising.

**DIRECTION FOR USE**

*THE TABLETS MUST BE SWALLOWED INTACT WITHOUT CRUSHING OR CHEWING.*

**OVERDOSAGE**

**Hemodynamic Effects**

Vasotrate-OD overdosage is associated with persistent throbbing headache, confusion, moderate fever, vertigo, palpitations, visual disturbances, nausea, vomiting, syncope, dyspnoea, diaphoresis, heart block, paralysis, coma, seizures and death. Prudent therapy in this situation should be directed toward an increase in central fluid volume. Passive elevation of patient's legs may sufficient, but intravenous infusion of normal saline may be necessary.

**Methaemoglobinaemia**

This has been reported in patients taking organic nitrates. The treatment of choice is methylene blue 1-2mg/kg intravenously.

**EXPIRY DATE**

Do not use later than the date of expiry.

**STORAGE**

Keep in a dry place at a temperature not exceeding 30°C, protected from light.

**PRESENTATION**

**Vasotrate 30-OD:** It is available as white to off-white coloured round, biconvex, film coated tablets with break line on one side, in blister strip of 7 tablets.

**Vasotrate 60-OD:** It is available as light yellow coloured round, biconvex, film coated tablets with break line on one side, in blister strip of 7 tablets.

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Manufactured by :
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