TRIMETAZIDINE DIHYDROCHLORIDE

VASTAREL® OD

80 mg Prolonged-release Capsule
Cardiac Therapy (Other Cardiac Preparations)

Product Description
Hard capsule with a white body and an orange red cap with a printed white Servier logo and "80" on it.

Formulation
One prolonged-release hard capsule contains 80 mg of trimetazidine dihydrochloride.
Excipient with known effect: Sucrose 33.75 mg per capsule.

Pharmacodynamics and Pharmacokinetics
Pharmacodynamics
By preserving energy metabolism in cells exposed to hypoxia or ischemia, trimetazidine prevents a decrease in intracellular ATP levels, thereby ensuring the proper functioning of ionic pumps and transmembrane sodium-potassium flow whilst maintaining cellular homeostasis.

Trimetazidine inhibits β-oxidation of fatty acids by blocking long-chain 3-ketoacyl-CoA thiolase, which enhances glucose oxidation. In an ischemic cell, energy obtained during glucose oxidation requires less oxygen consumption than in the β-oxidation process. Potentiation of glucose oxidation optimizes cellular energy processes, thereby maintaining proper energy metabolism during ischemia.

In patients with ischemic heart disease, trimetazidine acts as a metabolic agent, preserving the myocardial high-energy phosphate intracellular levels. Anti-ischemic effects are achieved without concomitant hemodynamic effects.

Pharmacokinetics
Absorption: After oral administration of trimetazidine 80 mg capsule, trimetazidine PK profile is flat with a peak of trimetazidine concentration reached around 14 hours after drug intake. Over dosing interval, i.e. 24 hours, the plasma concentration remains for 15 hours at levels above or equal to 75% of the maximum concentration. Steady state is reached by the third dose intake (3 days). Food intake has no effect on trimetazidine PK after administration of the 80 mg formulation.
Distribution: The volume of distribution is 4.8 l/kg; protein binding is low (16%).
Elimination: Trimetazidine is primarily eliminated in the urine, mainly as unchanged form. The elimination half-life is on average 7 hours in healthy young volunteers and 12 hours in elderly (more than 65 years).
Total clearance of trimetazidine mainly consists of renal clearance which is directly correlated to creatinine clearance and, to a lesser extent, of liver clearance which is reduced with age.

Special populations
Elderly: The elderly may have increased trimetazidine exposure due to age-related decrease in renal function. A dedicated pharmacokinetic study performed in elderly 75-84 years or very elderly (≥85 years) participants showed that moderate renal impairment (creatinine clearance between 30 and 60 ml/min) increased respectively by 1.0 and 1.3 fold the Trimetazidine exposure in comparison to younger participants (30-65 years) with moderate renal impairment.

A specific clinical study carried out in an elderly population (older than 75 years old) using a dosage of 2 tablets of trimetazidine MR 35 mg per day taken in 2 doses, analyzed by a kinetic population method, showed on average a 2-fold increase in plasma exposure in patients with severe renal impairment (creatinine clearance below 30 ml/min) as compared to those with a creatinine clearance above 60 ml/min.
No safety concern was observed in the elderly population as compared to the general population.

Renal impairment: Trimetazidine exposure is increased on average by 1.7-fold in patients with moderate renal impairment (creatinine clearance between 30 and 60 ml/min), and on average by 3.1-fold in patients with severe renal impairment (creatinine clearance below 30 ml/min) as compared to healthy volunteers, with normal renal function.
No safety concern was observed in this population as compared to the general population.

Pediatrics: The pharmacokinetics of trimetazidine has not been studied in the pediatric population (<18 years old).

Indication
Trimetazidine is indicated in adults as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled by or intolerant to first-line antianginal therapies.

Dosage and Administration
The dose is one capsule of 80 mg of trimetazidine once daily during breakfast.

The benefit of the treatment should be assessed after three months and trimetazidine should be discontinued if there is no treatment response.

Special populations
Patients with renal impairment: In patients with moderate renal impairment (creatinine clearance 30-60 ml/min), the recommended dose is reduced by half i.e., 1 tablet of 35 mg modified-release tablet in the morning during breakfast.

Elderly patients: Elderly patients may have increased trimetazidine exposure due to age-related decrease in renal function. In patients with moderate renal impairment (creatinine clearance 30-60 ml/min), the recommended dose is reduced by half i.e. 1 tablet of 35 mg modified-release tablet in the morning during breakfast. Dose titration in elderly patients should be exercised with caution.

Pediatric population: The safety and efficacy of trimetazidine in children aged below 18 years have not been established. No data are available.

Method of administration
Capsule must be taken orally without opening it, once daily i.e. one in the morning during breakfast.

Contraindications
- Hypersensitivity to the active substance or to any of the excipients,
- Parkinson disease, parkinsonian symptoms, tremors, restless leg syndrome, and other related movement disorders,
- Severe renal impairment (creatinine clearance < 30 ml/min).

Special warnings and precautions
This medicine is not a curative treatment for angina attacks, nor is it indicated as an initial treatment for unstable angina or myocardial infarction, nor in the pre-hospital phase or during the first days of hospitalization.
In the event of an angina attack, the coronaropathy should be reevaluated and an adaptation of the treatment considered (medicinal treatment and possibly revascularization).
Trimetazidine can cause or worsen parkinsonian symptoms (tremor, akinesia, hypertonia), which should be regularly investigated, especially in elderly patients. In doubtful cases, patients should be referred to a neurologist for appropriate investigations.
The occurrence of movement disorders such as parkinsonian symptoms, restless leg syndrome, tremors, gait instability should lead to definitive withdrawal of trimetazidine.
These cases have a low incidence and are usually reversible after treatment discontinuation. The majority of the patients recovered within 4 months after trimetazidine withdrawal. If parkinsonian symptoms persist more than 4 months after drug discontinuation, a neurologist opinion should be sought.
Falls may occur, related to gait instability or hypotension, in particular in patients taking antihypertensive treatment.

Caution should be exercised when prescribing trimetazidine to patients in whom an increased exposure is expected:
• moderate renal impairment,
• elderly patients older than 75 years old
This drug contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.

Pregnancy and lactation
Pregnancy:
There are no data from the use of trimetazidine in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of trimetazidine during pregnancy.
Breastfeeding:
It is unknown whether trimetazidine is excreted in human milk. A risk to the newborns/infants cannot be excluded. Trimetazidine should not be used during breastfeeding.
Fertility:
Reproductive toxicity studies have shown no effect on fertility in female and male rats.

Effects on ability to drive and use machines
Trimetazidine does not have hemodynamic effects in clinical studies, however cases of dizziness and drowsiness have been observed in post-marketing experience, which may affect ability to drive and use machines.

Interactions
No drug interactions have been identified.

Adverse Drug Reactions
Adverse reactions, defined as adverse events considered at least possibly related to trimetazidine treatment are listed below using the following convention frequency: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

System Organ Class	Frequency	Preferred Term
Nervous system disorders	Common	Dizziness, headache
	Not known	Parkinsonian symptoms (tremor, akinesia, hypertonia), gait instability, restless leg syndrome, other related movement disorders, usually reversible after treatment discontinuation
	Not known	Sleep disorders (insomnia, drowsiness)
Ear and labyrinth disorders	Not known	Vertigo
Cardiac disorders	Rare	Palpitations, extrasystoles, tachycardia
Vascular disorders	Rare	Arterial Hypotension, Orthostatic hypotension that may be associated with malaise, dizziness or fall, in particular in patients taking antihypertensive treatment, flushing
Gastrointestinal disorders	Common	Abdominal pain, diarrhea, dyspepsia, nausea and vomiting
	Not known	Constipation
Skin and subcutaneous tissue disorders	Common	Rash, pruritus, urticaria
	Not known	Acute generalized exanthematus pustulosis (AGEP), angioedema
General disorders and administration conditions	Common	Asthenia
Blood and lymphatic system disorders	Not known	Agranulocytosis Thrombocytopenia Thrombocytopenic purpura
Hepatobiliary disorders	Not known	Hepatitis

Reporting of Adverse Drug Reaction
For suspected adverse drug reaction, report to the FDA at **www.fda.gov.ph.**
Seek medical attention immediately at the first sign of any adverse drug reaction.

Overdose and Treatment
Limited information is available on trimetazidine overdose. Treatment should be symptomatic.

Storage Condition
Store at temperatures not exceeding 30°C.

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

Availability
Trimetazidine (Vastarel OD) 80 mg: Cold blister/Alu Foil x 10's (Box of 30s)

SERVIER

Manufactured by:
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