Trimetazidine

Vestar®

35 mg Modified Release Tablet

Cardiac Therapy (Fatty acid oxidation inhibitor)

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FORMULATION
Each Modified-release (MR) tablet contains:
Trimetazidine dihydrochloride ……..... 35 mg

PRODUCT DESCRIPTION
Vestar® 35 mg Modified-release Tablet: Pink, round, biconvex, film-coated tablet, plain on both sides

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS
Findings from *in vitro* and *ex vivo* studies have demonstrated that trimetazidine is beneficial for ischemia and heart failure by (1) improving metabolic efficiency by changing the source of ATP production to glucose oxidation which decreases the consequences of recurrent ischemia and enhances left ventricular performance, (2) protecting endothelial function by increasing endothelial nitric synthase activity and nitric oxide availability, (3) preserving mitochondrial function and energy metabolism thus reducing ischemic left ventricular dysfunction, (4) limiting intracellular acidosis, (5) limiting sodium and calcium accumulation, and (6) inhibiting neutrophil infiltration.

PHARMACOKINETICS
Trimetazidine is rapidly absorbed from the intestinal mucosa after oral administration. In 13 healthy volunteers, the mean peak plasma trimetazidine concentration (C_{max}; 53.6 mcg/L) was reached 1.8 hours after a single 20 mg (immediate release) oral dose. After twice daily administration of trimetazidine 20 mg for 15 days, C_{max} (84.8 mcg/L) was reached in 1.7 hours. The area under the plasma trimetazidine concentration-time curve ($AUC_{0-\infty}$) was 508.9 mcg·h/L after a single 20 mg dose and 831.4 mcg·h/L after repeated administration. Steady state levels were reached within 24 hours and remained stable for the study duration.

Trimetazidine is only weakly protein bound in plasma (~16%) and therefore is widely distributed throughout the body. In 11 healthy volunteers, the volume of distribution (Vd) of trimetazidine was 318.6 L after a 40 mg intravenous dose.

The elimination half-life of trimetazidine 20 mg is about 6 hours after single or repeated oral administration. More than 80% of an administered dose of trimetazidine is excreted in urine within 48 hours, with 62% of the drug eliminated unchanged. Eight metabolites have been detected in urine, however, little is known of their properties.

Comparative Bioavailability Study
Trimetazidine (Vestar®) 35 mg modified-release tablet was shown to have comparable bioavailability to the reference product (innovator) in adults under fasting conditions. After multiple oral administration of trimetazidine (Vestar®) 35 mg modified-release tablet, mean peak trimetazidine plasma concentration (C_{max}) at steady state (8th dosing interval) of 0.1 ± 0.01 mcg/mL was achieved within 4.78 ± 1.52 hours (T_{max}). The area under the plasma concentration time-curve (AUC_{0-24h}) at steady state was 1.07 ± 0.24 mcg·h/mL.

INDICATIONS
- Treatment of angina pectoris
- Long-term treatment of coronary insufficiency

DOSAGE AND MODE OF ADMINISTRATION
Usual Adult Dose: 1 tablet at mealtime in the morning and evening, or, as prescribed by a physician.
- The modified-release (MR) tablet should be swallowed whole with a glass of water. Do not chew or crush the MR tablet since this may cause inappropriate release and absorption of the drug.

CONTRAINDICATIONS
- Hypersensitivity to trimetazidine or any component of the product
- Parkinson's disease, parkinsonian symptoms, tremors, restless leg syndrome, and other movement-related disorders
- Severe renal impairment (creatinine clearance <30 mL/min)
- Pregnancy
- Breastfeeding

WARNINGS AND PRECAUTIONS
- Trimetazidine is not a curative treatment for angina attacks, nor an initial treatment for unstable angina pectoris. In the event of an angina attack, inform your physician. Tests may be required and treatment regimen may be modified.
- Trimetazidine is not a treatment for myocardial infarction.
- Trimetazidine can cause or worsen parkinsonian symptoms (tremor, akinesia, hypertonia), especially in elderly patients.
- Trimetazidine therapy should be stopped permanently in patients who develop movement disorders and neurological consultation sought if such adverse events persist for more than 4 months after discontinuation of the drug.
- Falls may occur, related to gait instability or hypotension, particularly in patients taking antihypertensive drugs.
- Trimetazidine should be used with caution in elderly patients and in patients with renal impairment.
- **Effects on Ability to Drive and Use Machine**
  Cases of dizziness and drowsiness have been observed in postmarketing experience, which may affect the ability to drive and use machines.

INTERACTIONS WITH OTHER MEDICAMENTS
Monoamine oxidase (MAO) inhibitors: Trimetazidine should not be coadministered with these drugs since non-interaction has not been established
Digoxin, phenazone, theophylline: No effect on the pharmacokinetics of trimetazidine

STATEMENT ON USAGE FOR HIGH RISK GROUPS
Pregnancy: Animal studies have not shown any teratogenicity. However, in the absence of clinical data and for safety reasons, trimetazidine should be avoided during pregnancy.
Lactation: In the absence of data on excretion of trimetazidine in breast milk, breastfeeding is not recommended during treatment.
Elderly: Elderly patients may have increased trimetazidine exposure due to age-related decrease in renal function. Caution is advised.
Children: The safety and efficacy of trimetazidine in patients below 18 years old have not been established.

UNDESIRABLE EFFECTS
The most frequently reported adverse events to trimetazidine are dizziness, headache, abdominal pain, diarrhea, dyspepsia, nausea and vomiting, rash, pruritus, urticaria, and asthenia.
Blood and lymphatic system: Agranulocytosis, thrombocytopenia, thrombocytopenic purpura

Nervous system disorders: Parkinsonian symptoms (tremor, akinesia, hypertonia), gait instability, restless leg syndrome, other movement-related disorders, sleep disorders (insomnia, drowsiness)
Cardiac disorders: Palpitations, extrasystoles, tachycardia
Vascular disorders: Arterial hypotension, orthostatic hypotension, flushing
Gastrointestinal disorders: Constipation
Hepatobiliary disorders: Hepatitis
Skin and subcutaneous tissue disorders: Acute generalized exanthematous pustulosis (AGEP), angioedema

OVERDOSE AND TREATMENT
In the event of trimetazidine overdosage, consult a physician immediately.

STORAGE CONDITION
Store at temperatures not exceeding 30°C.
Keep the product out of sight and reach of children.

ADVERSE DRUG REACTION REPORTING STATEMENT
For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph AND Unilab at (+632) 858-1000 or productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

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

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