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

TRIMET

(Trimetazidine dihydrochloride tablets 20 mg)

COMPOSITION
BRAND NAME: TRIMET
Each film coated tablet contains: Trimetazidine dihydrochloride Ph.Eur….20 mg
PROPERTIES
Trimetazidine (S 5016), is a cellular anti-isehemic agent. Its chemical name is I-(2,3,4-trimethoxybenzyl)-piperazine dihydrochloride. Initial pharmacological studies have indicated that trimetazidine prevents cellular changes associated with ischemia or hypoxia, but it has no effect under normoxic conditions.
Trimetazidine is freely soluble in water (80%), sparingly soluble in methanol, but insoluble in other organic solvents. Trimetazidine solution is slightly sensitive to light although substantially less than dihydropyridines. The molecular weight of trimetazidine is, as a dihydrochloride, 339.27 and, in basic form, 266.34. The molecule has two pKa values (4.32 and 8.95) and the pH value of an aqueous solution (5 mg/ml) is 3; this aqueous solution is stable at room temperature.
CLINICAL PHARMACOLOGY
MODE OF ACTION
By inhibiting fatty acid inhibits metabolism and secondarily stimulating glucose metabolism, trimetazidine optimizes cardiac metabolism and thus protects the heart against the harmful effects of ischaemia. However, the definitive mechanism of action of trimetazidine has yet to be determined.
Consistent with a cytoprotective effect, trimetazidine exhibited anti-ischaemic effects in vivo. It limited the extent of necrosis in a rat model of myocardial ischaemia and reduced the extent of nephropathy in a rat model of renal ischaemia. In addition, trimetazidine had a direct anti-ischaemic effect in patients undergoing coronary angioplasty.
PHARMACODYNAMICS
By preserving the 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 transmembranous sodium-potassium flow whilst maintaining cellular homeostasis.
In man: controlled studies in angina patients have shown that trimetazidine increases coronary flow reserve, thereby delaying the onset of ischemia associated with exercise, limits rapid swings in blood pressure without any significant variations in heart rate, significantly decreases the frequency of angina attacks, and leads to a significant decrease in the use of nitrates.
PHARMACOKINETICS
Absorption and Distribution
Trimetazidine is rapidly absorbed from the intestinal mucosa after oral administration. In 13 healthy volunteers, the mean peak plasma trimetazidine concentration (Cmax; 53.6 μg/L) was reached 1.8 hours after a single 20mg oral dose. After twice daily administration of trimetazidine 20mg for 15 days, Cmax (84.8 μg/L)was reached in 1.7 hours. The area under the plasma trimetazidine concentration-time curve (AUC0-∞) was 508.9μg/L • h after a single 20mg dose and 831.4 μg/ L • h after repeated administration. Steady-state levels were reached within 24 hours and remained stable for the study duration. The bioavailability of a 40mg tablet of trimetazidine in 11 healthy volunteers was 88.7% relative to an intravenous dose.
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 318.6L after a 40mg intravenous dose.
Metabolism and Elimination
The elimination half-life of trimetazidine 20mg is 6 hours after single or repeated oral administration. More than 80% of an administered dose of trimetazidine is excreted in the urine within 48 hours, with 62% of the drug eliminated unchanged. Eight metabolites (including 4 phase II metabolites) have been detected in urine, but little is known of their properties.
The total clearance of trimetazidine was 37.45 L/h after 40mg intravenous dose in 11 healthy volunteers.
SPECIAL POPULATIONS
Pediatric: There is no experience with trimetazidine in children.
Geriatric: Metabolic agents such as trimetazidine do not have hemodynamic actions and therefore represent useful alternative agents in the elderly, avoiding the adverse effects. In the elderly sub study of Trimpol-1 (Trimetazidine in Poland), trimetazidine significantly increased exercise duration, time to onset of angina, time to 1-mm ST-segment depression, and total work during maximal exercise testing. Importantly, there was also a significant reduction in anginal episodes and glyceryl trinitrate consumption, and minimal adverse effects. Combining a low-dose hemodynamic agent with trimetazidine may maximize symptom relief and minimize adverse events. Patients intolerant of hemodynamic agents may benefit from trimetazidine as monotherapy.
Renal and Hepatic impairment
No dosage adjustments are required in patients with impaired renal and hepatic function.

INDICATIONS
Trimetazidine is indicated in the treatment of ischemic heart disease (angina pectoris, sequelae of infarction).
CONTRAINDICATIONS
Hypersensitivity to trimetazidine
WARNINGS AND PRECAUTIONS
No drug interactions have so far been reported. In particular, no interactions of trimetazidine with beta-blockers, calcium antagonists, nitrates, heparin, hypolipidemic agents or digitalis have been reported.
PRECAUTIONS
Pregnancy
There is insufficient evidence to recommend the use of trimetazidine in pregnancy. Animal studies do not reveal any teratogenic effect
Lactation
There is no information on the secretion of trimetazidine into breast milk. However, breast-feeding should be discontinued if the use of trimetazidine is considered essential.
Pediatrics
There is no experience with trimetazidine in children.
ADVERSE REACTIONS
The most commonly encountered side effects are gastric discomfort, nausea, headache and vertigo.
DRUG INTERACTIONS
Oral trimetazidine 20mg twice daily for 25 days had no effects on the half-life of phenazone in 13 healthy male volunteers, indicating that the antianginal agent is neither an inducer nor an inhibitor of drug hydroxylation. In the same individuals, co-administration of trimetazidine 20mg had no effects on the pharmacokinetics of single oral doses of digoxin O.5mg or theophylline 5 mg.
DOSAGE AND METHOD OF ADMINISTRATION
Oral trimetazidine is indicated for the preventive treatment of anginal attacks. The recommended daily dosage of the drug is 40 or 60 mg (in 2 or 3 divided doses) which should be administered with meals.
EXPIRY DATE
Do not use later than the date of expiry.
STORAGE
Store below 30^{o}C.
PRESENTATION
TRIMET is available in strips of 10 tablets.

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Manufactured by:
TORRENT PHARMACEUTICALS LTD.
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