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

**Generic Name**

TRIMETAZIDINE DIHYDROCHLORIDE EXTENDED RELEASE TABLETS 35 MG

**Brand Name**

TRIVEDON MR

**Composition**

Trivedon MR
Each film coated extended release tablet contains:
Trimetazidine Dihydrochloride Ph.Eur …… 35 mg

**Dosage Form**

Tablets

**Product Description**

White to off-white circular biconvex, film coated tablets plain on both sides with aperture on one face.

**Pharmacology**

***Pharmacodynamics***

Trimetazidine is a unique anti-ischaemic drug, which protects the myocardial cell from the harmful effects of ischaemia.

The mode of action is trimetazidine is different from beta-blockers, calcium channel blockers and nitrates. Unlike these antianginal agents, which affect haemodynamic determinants of myocardial oxygen supply-demand balance, trimetazidine prevents the damage to the myocardial cell during an ischaemic episode. Trimetazidine inhibits fatty acid oxidation secondary to an inhibition of long-chain 3-ketoacyl CoA thiolase (KAT), resulting in an increase in glucose oxidation. This results in switching energy substrate preference from fatty acid oxidation to the more efficient glucose oxidation which explains the antianginal properties. Trimetazidine prevents intracellular metabolic changes such as depletion of adenosine triphosphate (ATP) and

phosphocreatinine, accumulation of protons, and toxic free radical generation which result from ischaemia and reperfusion in the myocardium.

Trimetazidine exerts protective effects against ionic disturbance due to ischemia- reperfusion in fatty acid-perfused hearts, but depending on the degree of severity. Trimetazidine has also been proven to provide membrane protection through a large increase in phospholipids turnover. This effect contributes to a reorganization of fatty acid utilization balance, resulting in their decreased availability for energy production. As such, trimetazidine raises cell tolerance to ischaemia-reperfusion injury. Trimetazidine enhances the metabolic status of cardiomyocytes in hypoperfused regions in patients with previous myocardial infarction as well as those with a history of angina.

***Pharmacokinetics***

Trimetazidine is absorbed through the intestinal mucosa with a Tmax (time to reach maximum concentration) of 5.4 hours. The Cmax is 89 microg/L. the t75 (time during which the plasma concentration remains above 75% of Cmax) is 11 hours. The bioavailability is 87%, slightly inferior with trimetazidine modified release than with the immediate-release formulation, explaining the increase in the dose of trimetazidine (35 mg compared with 20 mg for the immediate-release tablet). The bioavailability is not influenced by food. The steady state is reached 2 to 3 days after starting the treatment.

The volume of distribution, unaffected by the modified-release formulation, is 4.8 L/kg which means good tissue diffusion. Protein binding affinity is low (16%), with equal binding to albumin and alpha-glycoprotein. No uptake of trimetazidine in red blood cells was observed. The major drug related component observed in plasma and urine was unchanged trimetazidine. In addition to the parent drug, 10 metabolites were detected in urine. Seven routes of metabolism have been identified in man: 2 phase I oxidation and 5 phase II conjugation routes. Trimetazidine and its metabolites are predominantly eliminated in urine. A small proportion of trimetazidine is excreted in the faeces (about 6% of the administered dose). The renal trimetazidine clearance is 350 ml/min and is independent of the urine and plasma concentration of the drug, whereas it is correlated with renal creatinine clearance. That is why the elimination half-life is shorter in the healthy patient compared with the elderly patient (7 and 12 hours, respectively). Trimetazidine can be safely prescribed without adapting the dose in elderly patients and in case of renal insufficiency (if creatinine clearance remains above 15 ml/min).

**Indications**

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 anti-anginal therapies

**Dosage and Method of Administration**

The dose is one tablet of 35mg of trimetazidine twice daily during meals. The benefit of the treatment should be assessed after three months and trimetazidine should be discontinued if there is no treatment response.

***Special Population***

Patient with renal impairment*;*
In patients with moderate renal impairment (creatinine clearance [30-60] ml/min), the recommended dose is 1 tablet of 35mg in the morning during breakfast.

Elderly Patients
Elderly patient 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 1 tablet of 35mg in the morning during breakfast. Dose titration in elderly patients should be exercised with caution.

**Contraindications**

- Hypersensitivity to trimetazidine.
- Parkinson disease, parkinsonian symptoms, tremors, restless leg syndrome, and other related movement disorders
- Severe renal impairment (creatinine clearance < 30ml/min)

**Warnings and Precautions**

It is not a curative treatment for angina attacks, nor is it indicated as an initial treatment for unstable angina, or myocardial infarction.

In the event of an angina attack, the coronaropathy should be re-evaluated and an adaptation of the treatment considered (drug treatment and possibly revascularisation).

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.

Fall may occur, related to gait instability or hypotension, in particular in patients taking antihypertensive treatment.

Caution should be exercise when prescribing trimetazidine to patients in whom an increased exposure is expected:

- moderate renal impairment
- Elderly patients older than 75 years old

**Drug Interactions**

No drug interactions have been reported. In particular, no interactions have been reported with beta-blockers, calcium antagonists, nitrates, heparin, hypolidaemic agents or digitalis preparation.

**Pregnancy and lactation**

**Use in pregnancy & lactation:** No teratogenic effect was seen in animal studies; in the absence of clinical data, a risk of birth defect induction can not be excluded; consequently, as a precaution, it is best not to prescribe the drug during pregnancy.

In the absence of data on excretion of the drug in milk, breastfeeding is not recommended during treatment.

**Undesirable effects**

The most commonly encountered side effects are gastric discomfort, nausea, headache and vertigo. However, the side effects are mild and non-specific.

Nervous system disorders (Frequency not known) include Parkinsonian symptoms (tremor, akinesia, hypertonia), gait instability, restless leg syndrome, other related movement disorders usually reversible after treatment discontinuation.

**Overdose**

The experience of overdosage is very limited. Patients should be monitored in terms of cardiovascular and hemodynamic parameters.

**Incompatibilities**

None reported.

**Route of Administration**

Oral

**Shelf-Life**

36 months

**Storage and Handling Instruction**

Store below 30ºC

**Packaging Information**

Carton having 10 Blisters of 10 tablets each.

**Registration Holder in Malaysia**

Cipla Malaysia SDN BHD
Suite 1101, Amcorp Tower,
Amcorp Trade Centre, 18 Persiaran Barat,
46050 Petaling Jaya, Selangor, Malaysia

**Manufactured By**

Cipla Ltd.
L-139 to L-146,
Verna Industrial Estate, Verna
Salcette, Goa, India.

**Last Updated**

June 2020