TRIZEDON® MR

Trimetazidine 2 HCl

COMPOSITION

Trimetazidine dihydrochloride 35 mg.
Excipients: q.s. for one modified release film-coated tablet.

PHARMACEUTICAL FORM

Modified release film-coated tablet.

THERAPEUTIC INDICATION

Adjunctive to established antiangina. Should not be used as monotherapy.

POSOLOGY AND METHOD OF ADMINISTRATION

Oral route
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 populations

Patients with renal impairment
In patients with moderate renal impairment (creatinine clearance [30-60] ml/min) (see *Special warnings and precautions for use* and *Pharmacokinetic properties*), the recommended dose is 1 tablet of 35mg in the morning during breakfast.

Elderly patients
Elderly patients may have increased trimetazidine exposure due to age-related decrease in renal function (see section *Pharmacokinetic properties*). 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 (see *Special warnings and precautions for use*).

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

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)
- Use of this drug in nursing mothers is generally inadvisable.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

This drug is not a curative treatment for angina attacks, nor is it indicated as an initial treatment for unstable angina, nor myocardial infarction, nor in the pre-hospital phase or during the first days of hospitalisation.

In the event of an angina attack, the coronary heart disease should be reevaluated and an adaptation of the treatment considered (medicinal 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 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.

Severe cutaneous adverse reactions (SCARs)

Severe cutaneous adverse reactions (SCARs) including drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported in association with trimetazidine treatment. At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, trimetazidine should be withdrawn immediately and an alternative treatment considered (as appropriate).

Falls may occur, related to gait instability or hypotension, in particular in patients taking antihypertensive treatment (see *Side Effects)*.

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

- Moderate renal impairment (see *Posology and method of administration* and *Pharmacokinetic properties)*
- Elderly patients older than 75 years old (see *Posology and method of administration)*

In patients with severe hepatic failure, in the absence of specific studies, prescription of TRIZEDON® MR 35 mg is not recommended.

This medicinal product is generally not recommended during breastfeeding (see section *Pregnancy and Breastfeeding*).

Athletes: This medicinal product contains a drug substance that may give a positive result in anti-doping tests.

Pregnancy and Breast-feeding

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 (see section *Preclinical Safety Data*). As a precautionary measure, it is preferable to avoid the use of TRIZEDON® MR 35 mg during pregnancy.

Breast-feeding

It is unknown whether trimetazidine/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. TRIZEDON® MR 35 mg should not be used during breast-feeding.

Fertility
Reproductive toxicity studies have shown no effect on fertility in female and male rats (see section *Preclinical Safety Data*).

Effects on ability to drive and use machines

Not applicable.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

No drug interaction has been reported.

UNDESIRABLE EFFECTS

Concerning the adverse reactions associated with the use of trimetazidine, also see section *Special Warnings and Precautions For Use*.
The table below includes the adverse reactions from spontaneous notifications and scientific literature.
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
	Uncommon	Paraesthesia
	Not known	Parkinsonian symptoms (tremor, akinesia, hypertonia), gait instability, restless leg syndrome, other related movement disorders, usually reversible after treatment discontinuation Sleep disorders (insomnia, drowsiness)
Cardiac disorders	Rare	Palpitations, extrasystoles, tachycardia
Vascular disorders	Rare	Arterial hypotension, orthostatic hypotension that may be associated with malaise, dizziness, or a fall, in particular in patients taking antihypertensive treatment, flushing
Ear and labyrinth disorders	Not known	Vertigo
Gastrointestinal disorders	Common	Abdominal pain, diarrhoea, dyspepsia, nausea and vomiting
	Not known	Constipation
Skin and subcutaneous tissue disorders	Common	Rash, pruritus, urticaria
	Not known	Drug reaction with eosinophilia and systemic symptoms (DRESS), Acute generalized exanthematus pustulosis (AGEP) (see section SPECIAL WARNINGS AND PRECAUTIONS FOR USE) , angioedema
General disorders and administration site conditions	Common	Asthenia
Blood and lymphatic system disorders	Not known	Agranulocytosis Thrombocytopenia Thrombocytopenic purpura
Hepatobiliary disorders	Not known	Hepatitis

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via via PUSAT FARMAKOVIGILANS-BPOM: Tlp. 021-4245459, 021-4244755 Ext. 111, Fax. 021-4243605, 021-42885404; Email: pv-center@pom.go.id and/or Indonesia-MESO-BadanPOM@hotmail.com.

Overdose

The information available concerning trimetazidine overdose is limited. Treatment should be symptomatic.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

OTHER CARDIAC PREPARATIONS Code ATC: C01EB15
(C: cardiovascular system)

Mechanism of action
By preserving energy metabolism in cells exposed to hypoxia or ischaemia, 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 ischaemic 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 ischaemia.
Pharmacodynamic effects

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

Clinical studies on trimetazidine have demonstrated its efficacy and safety in the treatment of patients with chronic angina, either alone or when the benefit from other antianginal medicinal products was insufficient.
In a 426-patients randomized, double blind, placebo-controlled study (TRIMPOL-II), trimetazidine (60mg/day) added to metoprolol 100mg daily (50 mg b.i.d) for 12 weeks significantly improved statistically exercise tests parameters and clinical symptoms as compared to placebo: total exercise duration +20.1s, p= 0.023, total workload +0.54 METs, p=0.001, time to 1-mm ST-segment depression +33.4s, p=0.003, time to onset of angina +33.9s, p<0.001, angina attacks/week -0.73, p=0.014 and short acting nitrates consumption/week, -0.63, p=0.032, without hemodynamic changes.
In a 223 patients randomized, double blind, placebo-controlled study (Sellier), one 35 mg trimetazidine modified release tablet (b.i.d.) added to 50 mg atenolol (o.d.) for 8 weeks produced a significant increase (+34.4s, p=0.03) in the time to 1-mm ST-segment depression in exercise tests, in a sub-group of patients (n=173), when compared to placebo, 12 hours after taking the drug. A significant difference was also evidenced for the time to onset of angina pectoris (p=0.049). No significant difference between groups could be found for the other secondary endpoints (total exercise duration, total workload and clinical endpoints).

Pharmacokinetic properties

- After oral administration, maximum concentration is found, on average, 5 hours after taking the tablet. Over 24 hours the plasma concentration remains at levels above or equal to 75% of the maximum concentration for 11 hours.
  Steady state is reached by the 60th hour, at the latest.
- The pharmacokinetic characteristics of Trizedon MR are not influenced by meals.
- The apparent distribution volume is 4.8 l/kg; protein binding is low: in vitro measurements give value of 16%.

- Trimetazidine is eliminated primarily in the urine, mainly in the unchanged form.
  The elimination half-life of Trizedon MR is an average of 7 hours in healthy young volunteers and 12 hours in subjects aged more than 65 years. Total clearance of trimetazidine is the result of major renal clearance which is directly correlated to creatinine clearance and, to a lesser extent, to liver clearance which is reduced with age.

Special populations

Elderly subjects
A specific clinical study carried out in an elderly population using a dosage of 2 tablets per day taken in 2 doses, analysed by a population pharmacokinetics approach, showed an increase in plasma exposure.
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.

Renal impairment
Trimetazidine exposure is increased on average by 1.7 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 young volunteers, with normal renal function. No safety concerns were observed in this population as compared with the general population.

Paediatric population
The pharmacokinetics of trimetazidine has not been studied in the paediatric population (<18 years).

Preclinical safety data
Chronic oral toxicity studies in dogs and rats showed a good safety profile.
Genotoxic potential was assessed in in vitro studies, including evaluation of the mutagenic and clastogenic potential, and in one in vivo study. All the tests were negative.

Reproductive toxicity studies performed in mice, rabbits and rats showed no embryotoxicity or teratogenicity. In rats, fertility was not impaired and no effects on postnatal development were observed.

LIST OF EXCIPIENTS
Calcium hydrogen phosphate dihydrate, hypomelosa; povidone; silica colloid anhydrate, magnesium stearate, titanium dioxide, glycerol, hypomelosa, macrogol 6000, red iron oxide.

STORAGE CONDITIONS

Store Below 30°C
Shelf life : 3 years

PACK SIZE
Box of 60 modified release film-coated tablets (2 blister of 30 tablets).

Reg. No : DKL1604524514A1

HARUS DENGAN RESEP DOKTER

Manufactured by :

PT. Darya-Varia Laboratoria Tbk

Under license of :

Les Laboratoires Servier
France

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