VASTAREL MR

INN: Trimetazidine

1. NAME OF THE MEDICINAL PRODUCT

VASTAREL MR, modified release film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Trimetazidine dihydrochloride…….35 mg
Excipients q.s. for one modified release film-coated tablet.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL form

Modified release film-coated tablet

4. Clinical particulars

4.1 Therapeutic 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 antianginal therapies.

4.2 Dosage and method of administration

Dosage

Oral route.

The dose is one tablet of trimetazidine 35 mg twice daily, i.e. once in the morning and once in the evening, 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 sections 4.4 and 5.2), 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 5.2). 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 section 4.4).

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

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Parkinson disease, parkinsonian symptoms, tremors, restless leg syndrome, and other related movement disorders,
- Severe renal impairment (creatinine clearance < 30ml/min).

4.4 Special warnings and precautions for use

This medicinal product is generally not recommended during breastfeeding (see section 4.6).

This medicinal product 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 nor during the first days of hospitalisation.

In the event of an angina attack, the coronaropathy 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 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 (see section 4.8).

Caution should be exercised when prescribing trimetazidine to patients in whom an increased exposure is expected:
- moderate renal impairment (see sections 4.2 and 5.2),
- elderly patients older than 75 years old (see section 4.2)

This medicinal product is generally not recommended during breastfeeding (see section 4.6).

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

4.5 Interaction with other medicinal products and other forms of interaction

No drug interaction has been reported.

4.6 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 5.3). As a precautionary measure, it is preferable to avoid the use of VASTAREL during pregnancy.

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

Fertility
Reproductive toxicity studies have shown no effect on fertility in female and male rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Trimetazidine does not have haemodynamic effects in clinical studies, however cases of dizziness and drowsiness have been observed in post-marketing experience (see section 4.8), which may affect ability to drive and use machines.

4.8 Side effects

Concerning the adverse reactions associated with the use of trimetazidine, also see section 4.4.

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
	Not known	Parkinsonian symptoms (tremor, akinesia, hypertonia), gait instability, restlessleg 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, diarrhoea, 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

4.9 Overdosage

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

OTHER CARDIOVASCULAR ANTIANGINAL DRUG 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 have demonstrated the efficacy and safety of trimetazidine in the treatment of patients with chronic angina, 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).

In a 1962 patients three-month randomised, double-blinded study (Vasco study) on top of atenolol 50 mg/d, two dosages of trimetazidine (70 mg/d and 140 mg/d) were tested versus placebo. In the overall population, including both asymptomatic and symptomatic patients, trimetazidine failed to demonstrate a benefit on both ergometric (total exercise duration, time to onset of 1mm ST and time to onset angina) and clinical endpoints. However, in the subgroup of symptomatic patients (n= 1574) defined in a post-hoc analysis, trimetazidine (140 mg) significantly improved total exercise duration (+23.8 s versus +13.1 s placebo; p=0.001) and time to onset of angina (+46.3 s versus +32.5 s placebo; p=0.005).

5.2 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 Vastarel 35mg 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 Vastarel 35mg 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).

5.3 Preclinical safety data

Chronic toxicity studies conducted by the oral route in dogs and rats, showed a good safety profile.
The genotoxic potential was assessed in in vitro studies, including evaluation of the mutagenic and clastogenic potential, and one in vivo study. All the tests were negative.
Reproductive toxicity studies in mice, rabbits and rats showed no embryotoxicity or teratogenicity. In rats, fertility was not impaired and there was no effects on postnatal development.

6. PHARMACEUTICAL DATA

6.1 List of excipients

Calcium hydrogen phosphate dihydrate; hypromellose; povidone; anhydrous colloidal silica, magnesium stearate;

Film-coating: titanium dioxide (E 171), glycerol, hypromellose, macrogol 6000, red iron oxide (E 172), magnesium stearate.

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

3 years.

6.4 Special precautions for storage

Below 30°C

6.5 Nature and contents of container

Aluminium/PVC blister packed in cardboard boxes.
Pack sizes – containing 60 tablets

Product Registration Holder:
Servier Malaysia Sdn Bhd
Unit No.25-02, Level 25, Imazium
No.8, Jalan SS21/37, Damansara Uptown
47400 Petaling Jaya, Selangor Darul Ehsan

Manufacturer:
Kotra Pharma (M) Sdn Bhd
No.1, 2 & 3, Jalan TTC 12,
Cheng Industrial Estate
75250 Melaka

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