VASTAREL MR
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

VASTAREL 35 mg, modified-release film-coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Trimetazidine dihydrochloride..... 35.00 mg
For one 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. Posology and method of administration

Posology

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 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.

Method of administration

Tablets must be taken orally twice daily, *i.e*., one in the morning and one in the evening during meals.

4.3. Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Parkinson disease, parkinsonian symptoms, tremors, restlessleg 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 lactation (see Pregnancy and Lactation).

This medicine is not a curative treatment for angina attacks, nor is it indicated as an initial treatment for unstable angina or myocardial infarction, nor in the pre-hospital phase or 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, restlessleg syndrome, tremors, gait instability should lead to definitive withdrawal of trimetazidine.
These cases have a low prevalence 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)

4.5. Interaction with other medicinal products and other forms of interaction

Not applicable

4.6 Fertility, pregnancy and lactation

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 trimetazidine during pregnancy.

Breastfeeding:
It is unknown whether trimetazidine is excreted in human milk. A risk to the newborns/infants cannot be excluded. Trimetazidine should not be used during breast-feeding.

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. Undesirable effects

Adverse reactions, defined as adverse events considered at least possibly related to trimetazidine treatment are listed below using the following convention frequency: 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)
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. Overdose

Not applicable

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Other cardiovascular antianginal drug, ATC code: C01EB15

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, 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).

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

By oral route, maximum concentration is observed, on average, 5 hours after taking the tablet. Over 24 hours, the plasma concentration is maintained at concentrations greater than or equal to 75% of the maximum concentration for 11 hours.

Steady state is reached by the 60th hour, at the latest.
• The pharmacokinetic properties of Vastarel 35 mg are not influenced by meals.
• The apparent distribution volume is 4.8 l/kg, trimetazidine protein binding is low: its value measured in vitro is 16%.
• Trimetazidine is eliminated primarily in the urine, mainly in the unaltered form.
The elimination half-life of Vastarel 35 mg is, on average, 7 hours in young healthy volunteers, and 12 hours in subjects over the age of 65.
Total clearance of trimetazidine is the result of major renal clearance, which is directly correlated to creatinine clearance and, to a lesser extent, to hepatic clearance, which reduces with age.
• A specific clinical study, performed in an elderly population, at a dosage of 2 tablets per day taken in 2 doses, analysed by a kinetic population method, showed an increase in plasma exposure.

5.3. Preclinical safety data

Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Calcium hydrogen phosphate dihydrate, hypromellose, povidone, anhydrous colloidal silica, magnesium stearate, macrogol 6000.

Film coating: titanium dioxide (E 171), glycerol, hypromellose, macrogol 6000, red iron oxide (E172), magnesium stearate.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

No special precautions for storage.

6.5. Nature and contents of container

10, 20, 28, 30, 56, 60, 90, 100 or 120 tablets in blister packs (PVC/Aluminium)

6.6. Special precautions for disposal and other handling

No special requirements for disposal

7. MARKETING AUTHORISATION HOLDER

LES LABORATOIRES SERVIER
50 RUE CARNOT
92284 SURESNES CEDEX
FRANCE

8. MARKETING AUTHORISATION NUMBERS

• 357 240-6 : 10 tablets in blister packs (PVC/Aluminium)
• 357 241-2 : 20 tablets in blister packs (PVC/Aluminium)
• 357 242-9 : 28 tablets in blister packs (PVC/Aluminium)
• 357 243-5 : 30 tablets in blister packs (PVC/Aluminium)
• 357 244-1 : 56 tablets in blister packs (PVC/Aluminium)
• 357 245-8 : 60 tablets in blister packs (PVC/Aluminium)
• 357 246-4 : 90 tablets in blister packs (PVC/Aluminium)
• 357 247-0 : 100 tablets in blister packs (PVC/Aluminium)
• 357 248-7 : 120 tablets in blister packs (PVC/Aluminium)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Initial marketing authorization: 06/08/2001.

Last renewal of marketing authorization: 27/03/2007.

10. DATE OF REVISION OF THE TEXT

03/09/2012

11. DOSIMETRY

Not applicable.

12. INSTRUCTIONS FOR THE PREPARATION OF RADIOPHARMACEUTICALS

Not applicable.

PRESCRIBING AND DISPENSING CONDITIONS

List II.