SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

VASTAREL MR, modified-release film-coated tablet.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Trimetazidine dihydrochloride.....35.00 mg
For one film-coated tablet.

For the 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

Oral route.
The dose is one tablet of 35 mg of trimetazidine 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 35 mg 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 35 mg 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 trimetazidine or to any of the excipients listed in section 6.1.
- Parkinson's disease, parkinsonian symptoms, tremors, restless leg syndrome, and other related movement disorders.
- Severe renal impairment (creatinine clearance < 30 mL/min).

4.4 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 or myocardial infarction. It should not be used 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 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 or 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 patients recover 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).

4.5 Interaction with other medicinal products and other forms of interaction

No drug interactions have been identified.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is 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.

Breastfeeding
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 breastfeeding.

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 did not show any 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 the ability to drive and use machines.

4.8 Undesirable effects

Concerning the adverse reactions associated with the use of trimetazidine, see also 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	Undesirable effects
Nervous system disorders	Common	Dizziness, headache
	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)
Ear and labyrinth disorders	Not known	Vertigo
Cardiac disorders	Rare	Palpitations, extrasystoles, tachycardia
Vascular disorders	Rare	Hypotension, orthostatic hypotension that may be associated with malaise, vertigo 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 generalised exanthematous pustulosis (AGEP), 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 the national reporting system.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

OTHER CARDIAC PREPARATIONS, ATC code: 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 ion 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 optimises 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-ischaemic 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 in combination with other antianginal treatments in poorly controlled patients.

In a 426-patient, randomised, double blind, placebo-controlled study (TRIMPOL-II), trimetazidine (60 mg/day) added to metoprolol 100 mg daily (50 mg b.i.d.) for 12 weeks statistically significantly improved exercise tests parameters and clinical symptoms as compared to placebo: total exercise duration +20.1 s, p=0.023, total workload +0.54 METs, p=0.001, time to 1-mm ST-segment depression +33.4 s, p=0.003, time to onset of angina +33.9 s, p<0.001, frequency of angina attacks/week -0.73, p=0.014 and short acting nitrates consumption/week, -0.63, p=0.032, without haemodynamic changes.

In a 223-patient, randomised, 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 (+34.4 s, 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 1,962-patient, three-month, randomised, double blind study (Vasco study) on top of atenolol 50 mg/d, two doses 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 1-mm ST-segment depression and time to onset of angina) and clinical endpoints. However, in the subgroup of symptomatic patients (n=1,574) 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 (+43.6 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 are not influenced by meals.
- The apparent distribution volume is 4.8 L/kg; trimetazidine protein binding is low: *in vitro* measurements give a value of 16%.
- Trimetazidine is eliminated primarily in the urine, mainly in the unchanged form.
  The elimination half-life of VASTAREL is on average 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 posology of 2 tablets per day taken in 2 doses, analysed by a population kinetics approach, showed an increase in plasma exposure. Trimetazidine exposure may be increased in elderly patients due to an age-related decrease in renal function. A pharmacokinetics study performed specifically in elderly (75-84 years) and very elderly (≥ 85 years) participants showed that in the event of moderate renal impairment (creatinine clearance between 30 and 60 mL/min) trimetazidine exposure was increased by a factor of 1.0 and 1.3 respectively in comparison with younger participants (30-65 years) with moderate renal impairment.

Renal impairment

On average, trimetazidine exposure is multiplied by 1.7 in patients with moderate renal impairment (creatinine clearance between 30 and 60 mL/min) and by 3.1 in patients with severe renal impairment (creatinine clearance below 30 mL/min) compared with 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 have not been studied in the paediatric population (< 18 years).

5.3 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium hydrogen phosphate dihydrate, hypromellose, povidone, anhydrous colloidal silica, magnesium stearate.
Film coating: titanium dioxide (E171), 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

Store below 30°C.

6.5 Nature and contents of container

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

Not all pack sizes may be marketed.

7. MARKETING AUTHORISATION HOLDER

LES LABORATOIRES SERVIER
50 RUE CARNOT
92284 SURESNES
FRANCE

10. DATE OF REVISION OF THE TEXT

09.2017