

ANNEX I

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 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 renal impairment (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 nor 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 postural 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 treatment discontinuation, a neurologist opinion should be sought.

Falls may occur, related to postural 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),
- Patients older than 75 years (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 identified.

4.6. Fertility, pregnancy and lactation

Pregnancy

There is no data on the use of trimetazidine in pregnant women. Studies performed in animals have not revealed direct or indirect harmful effects on reproduction (see section 5.3). As a precautionary measure, it is preferable to avoid the use of VASTAREL during pregnancy.

Breast-feeding

It is not known whether trimetazidine/metabolites are excreted in breast 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 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 ($\geq 1/10$), common ($\geq 1/100, < 1/10$), uncommon ($\geq 1/1000, < 1/100$), rare ($\geq 1/10,000, < 1/1000$), 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), postural 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: French National Agency for Medicines and Health Products Safety (ANSM) and Pharmacovigilance Regional Centres network, website: www.signalement-sante.gouv.fr.

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.

It thereby ensures the proper function of ion pumps and transmembrane sodium-potassium flow while maintaining cellular homeostasis.

Trimetazidine inhibits β -oxidation of fatty acids by blocking 3-ketoacyl-CoA thiolase, thus stimulating glucose oxidation. The energy generated in the ischaemic cell by glucose oxidation requires less oxygen consumption

than β -oxidation. Potentiation of glucose oxidation optimises cellular energy processes, thereby maintaining an adequate energy metabolism during ischaemia.

Pharmacodynamic effects

In patients with ischaemic heart disease, trimetazidine acts as a metabolic agent, preserving 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 combined 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 tolerance test 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 onset of 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 nitrate 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 demonstrated for the time to onset of angina pectoris ($p=0.049$). No significant difference between groups could be found for the 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 patients

A specific clinical study, performed in an elderly population, using a posology of 2 tablets per day taken in 2 doses, analysed by a kinetic population 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 volunteers with normal renal function. No safety problem was 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 performed 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

No special precautions for storage.

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.

6.6. Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

LES LABORATOIRES SERVIER

50 RUE CARNOT
92284 SURESNES
FRANCE

8. MARKETING AUTHORISATION NUMBER(S)

- 34009 357 240 6 9: 10 tablets in blisters (PVC/Aluminium)
- 34009 357 241 2 0: 20 tablets in blisters (PVC/Aluminium)
- 34009 357 242 9 8: 28 tablets in blisters (PVC/Aluminium)
- 34009 357 243 5 9: 30 tablets in blisters (PVC/Aluminium)
- 34009 357 244 1 0: 56 tablets in blisters (PVC/Aluminium)
- 34009 357 245 8 8: 60 tablets in blisters (PVC/Aluminium)
- 34009 357 246 4 9: 90 tablets in blisters (PVC/Aluminium)
- 34009 357 247 0 0: 100 tablets in blisters (PVC/Aluminium)
- 34009 357 248 7 8: 120 tablets in blisters (PVC/Aluminium)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[to be completed subsequently by the holder]

10. DATE OF REVISION OF THE TEXT

[to be completed subsequently by the holder]

11. DOSIMETRY

Not applicable.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Not applicable.

GENERAL CLASSIFICATION FOR SUPPLY

List I. Medicinal products subject to medical prescription

Initial annual prescription reserved for specialists in cardiology. Unrestricted renewal.