

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

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

Dosage

The dose is one tablet of trimetazidine 35 mg 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 one 35 mg tablet 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 one 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 trimetazidine 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 < 30 ml/min).

4.4 Special warnings and precautions for use

This medicinal product 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, 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).

4.5 Interaction with other medicinal products and other forms of interaction

Not applicable.

4.6 Pregnancy and lactation

Pregnancy

Studies in animals have not demonstrated a teratogenic effect; however, in the absence of clinical data, the risk of malformation cannot be excluded. Therefore, for safety reasons, prescription should be avoided during pregnancy.

Lactation

In the absence of data on excretion in breast milk, breastfeeding is not recommended during treatment.

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

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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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, 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 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 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 authorization 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: Agence nationale de sécurité du médicament et des produits de santé (Ansm) et réseau des Centres Régionaux de Pharmacovigilance. Site internet : www.ansm.sante.fr

4.9 Overdose

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

OTHER CARDIOVASCULAR ANTIANGINAL DRUG, 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 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 (60 mg/day) added to metoprolol 100 mg 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 35 mg 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.

- 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 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.

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

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

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

6.6 Special precautions for disposal and handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

LES LABORATOIRES SERVIER

50, RUE CARNOT
92284 SURESNES CEDEX
FRANCE

8. MARKETING AUTHORISATION NUMBER(S)

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

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

[for completion by the MAH]

10. DATE OF REVISION OF THE TEXT

[for completion by the MAH]

11. DOSIMETRY

Not applicable.

12. INSTRUCTIONS FOR THE PREPARATION OF RADIOPHARMACEUTICALS

Not applicable.

PRESCRIPTION AND DISPENSING CONDITIONS

List II.