

## 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 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).

**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 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 ( $\geq 1/10$ ); 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 | 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<br>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<br>Thrombocytopenia<br>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  $\beta$ -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  $\beta$ -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 60<sup>th</sup> 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 ( $\geq 85$  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.

#### **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

### **10. DATE OF REVISION OF THE TEXT**

03.2021