PACKAGE INSERT

1. NAME OF THE MEDICINAL PRODUCT

VASTAREL, film-coated tablets

2. QUALITATIVE AND QUANTITIVE COMPOSITION

Trimetazidine dihydrochloride…….20 mg
Excipients q.s. for one film-coated tablet
For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

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 use.

Method of administration
The dose is one tablet of 20 mg of trimetazidine three times a day 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 20 mg twice daily, i.e., one in the morning and one in the evening during meals.

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 20 mg twice daily, i.e., one in the morning and one in the evening during meals.

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 the active substance or to any of the excipients;
- Parkinson disease, parkinsonian symptoms, tremors, restless leg syndrome, and other related movement disorders;
- Severe renal impairment (creatinine clearance < 30ml/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 coronaropathy 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, 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 section4.8).

Caution should be exercised when prescribing trimetazidine to patients in whom an increased exposure is expected:
- moderate renal impairment (see sections4.2 and 5.2),
- elderly patients older than 75 years old (see section4.2)

This drug contains sunset yellow FCF S (E110) and cochineal red A (E 124) and may cause allergic reactions.

For athletes, this drug contains an active substance which may give a positive reaction in doping tests.

4.5 Interaction with other medicinal products and other forms of interaction

No drug interaction has been reported.

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. 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 breast-feeding.

Fertility
Reproductive toxicity studies have shown no effect on fertility in female and male rats

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 are listed below using the following convention: 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, restless leg syndrome, other related movement disorders, usually reversible after treatment discontinuation
	Not known	Sleep disorders (insomnia, drowsiness)
Ear and labyrinth disorders	Not known	Vertigo
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	Common	Rash, pruritus, urticaria.

disorders	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

Limited information is available on trimetazidine overdose. Treatment should be symptomatic.

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, absorption of trimetazidine is rapid and the plasma peak is reached in less than 2 hours.

After a single oral dose of 20 mg of trimetazidine, the peak plasma concentration is about 55 $ng.ml^{-1}$.

During repeated administration, the steady state is reached after 24 to 36 hours and remains very stable throughout treatment.

The apparent distribution volume is 4.8 l/kg which suggests good tissue diffusion. 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 is approximately 6 hours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet:
HPMC
MAGNESIUM STEARATE
MANNITOL
PEG
PVP
STARCH

TALC

Film-coating:
GLYCERIN
SUNSET YELLOW
TITANIUM DIOXIDE
PONCEAU 4R

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at room temperature, below 30°C

6.5 Nature and contents of container

10 or 60 tablets in blisters (PVC/Aluminium).

Not all pack sizes may be marketed.

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Manufacturer:
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