

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 20 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 20mg trimetazidine

Also contains ponceau 4R aluminium lake (E124), sunset yellow aluminium lake (E110)

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film coated tablet.

Product imported from Greece:

Round red, 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

Oral administration.

The dose is one tablet of 20mg of trimetazidine three times a day during meals.

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 20mg 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 20mg 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 listed in section 6.1.
- 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 indicated as an initial treatment for unstable angina, or myocardial infarction. It should not be used in the prehospital phase nor during the first days of hospitalisation.

In the event of an angina attack, angina pectoris disease should be reevaluated and an adaptation of the treatment considered.

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)

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:

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

Trimetazidine may cause the following undesirable effects ranked under the following frequency :

Very common (>1/10); common (>1/100, <1/10); uncommon (>1/1000, <1/100); rare (>1/10000, <1/1000); very rare

(<1/10000),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, restlessleg syndrome, other related movement disorders, usually reversible after treatment discontinuation
	Not known	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 conditions	Common	Asthenia
Blood and lymphatic system disorders	Not known	Agranulocytosis Thrombocytopenia Thrombocytopenic purpura
Hepatobiliary disorders	Not known	Hepatitis

Because of the presence of sunset yellow FCF S (E 110) and cochineal red A (E 124) in Vastarel 20mg, film-coated tablet, risk of allergic reactions.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Very limited information is available on Trimetazidine overdose. Treatment should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group : Other cardiovascular antianginal drug.

ATC code : C01EB15 (C: cardiovascular system).

Mechanism of action

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 (60mg/day) added to metoprolol 100mg 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

It is well absorbed and metabolised in the liver to inactive metabolites, then excreted in urine with a $T_{1/2}$ of 5-6 hours.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
Mannitol
Povidone
Magnesium stearate
Talc
Film coating
Glycerol
Hypromellose
Macrogol 6000
Magnesium stearate

Ponceau 4R aluminium lake (E124)
Sunset yellow FCF aluminium lake (E110)
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf life expiry date of this product shall be the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Overlabelled cardboard cartons containing 60 tablets in 4 overlabelled PVC/Aluminium blister strips.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

B&S Healthcare
Unit 4
Bradfield Road
Ruislip
Middlesex
HA4 0NU
UK

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA1328/212/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17th October 2014

10 DATE OF REVISION OF THE TEXT