Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Vastarel 20 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20 mg trimetazidine dihydrochloride.

Excipients with known effect:
Ponceau 4R aluminium lake (E124): 0.369 mg per tablet.
Sunset yellow FCFS(E110): 0.042 mg per tablet.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
Red, film-coated tablets.

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.

Posology
The dose is one tablet of 20mg of trimetazidine three times a day during meals.
Special populations
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
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 medicine is not a curative treatment for angina attacks, nor is indicated as an initial treatment for unstable angina or myocardial infarction nor in the prehospital 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.
Severe cutaneous adverse reactions (SCARs)
Severe cutaneous adverse reactions (SCARs) including drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported in association with trimetazidine treatment. At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, trimetazidine should be withdrawn immediately and an alternative treatment considered (as appropriate).

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)ExcipientsVastarel 20mg tablet contains sunset yellow FCF S (E 110) and ponceau 4R aluminium lake (E124), it may cause allergic reactions. Athletes:

This medicine 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 interactions have been identified.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data from the use of trimetazidine in pregnant women. Animals 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 breast-feeding.

Fertility
Reproductive toxicity studies have shown no effect on fertility of female or male rats (see section 5.3).

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

Tabulated list of adverse reactions
Trimetazidine may cause the following undesirable effects ranked under the following frequency :
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10000 to <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
	Uncommon	Paraesthesia
	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)
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 disorders	Common	Rash, pruritus, urticaria.
	Not known	Drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematus pustulosis (AGEP) (see section 4.4), angioedema
General disorders and administration 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 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

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
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 (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

Absorption
After oral administration, trimetazidine is rapidly and completely absorbed and the peak plasma concentration is reached in less than 2 hours. During repeated administration, steady state is reached after 24 to 36 hours.

Distribution
The apparent distribution volume is 4.8 l / kg; protein binding is low: in vitro measurements give value of 16%.

Elimination
Trimetazidine is eliminated primarily in the urine, mainly in the unchanged form. The elimination half-life is about 6 hours.

Linearity
Trimetazidine pharmacokinetics are linear following single dose administration up to 100 mg. Repeated doses showed a time-linear pharmacokinetic response.

Special populations

Elderly:
The elderly may have increased trimetazidine exposure due to age-related decrease in renal function. A dedicated pharmacokinetic study performed with trimetazidine MR 35mg in elderly (75-84 years) or very elderly (≥85years) participants showed that moderate renal impairment (creatinine clearance between 30 and 60 ml/min) increased respectively by 1.0 and 1.3 fold the Trimetazidine exposure in comparison to younger participants (30-65 years) with moderate renal impairment (see section 4.2).

A specific clinical study carried out in an elderly population (older than 75 years old) using a dosage of 2 tablets of trimetazidine MR 35mg per day taken in 2 doses, analysed by a kinetic population method, showed on average a 2-fold increase in plasma exposure in patients with severe renal impairment (creatinine clearance below 30ml/min) as compared to those with a creatinine clearance above 60 ml/min.
No safety concern was observed in the elderly population as compared to the general population.

Renal impairment
Trimetazidine exposure is increased on average by 1.7-fold in patients with moderate renal impairment (creatinine clearance between 30 and 60 ml/min), and on average by 3.1-fold in patients with severe renal impairment (creatinine clearance below 30ml/min) as compared to healthy volunteers, with normal renal function (see sections 4.2 and 4.3).

No safety concern was observed in this population as compared to the general population.

Paediatric population
The pharmacokinetics of trimetazidine have not been studied in the paediatric population (<18 years old).

5.3 Preclinical safety data

Chronic toxicity studies conducted by the oral route in dogs (5 to 40 mg.kg-1.d-1) and rats (5 to 200 mg.kg-1.d-1), showed a good safety profile.
Neither embryo-foetotoxic effects nor teratogenicity were detected in mice and in rabbits. The general study on reproduction and embryogenesis in 3 generations of rats showed no anomalies. The genotoxic potential was thoroughly assessed with three in vitro studies including the evaluation of the mutagenic and clastogenic potential and one in vivo study. All tests were negative.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
Mannitol
Povidone 7
Magnesium stearate
Talc

Film coating
Glycerol
Hypromellose
Macrogol 6000

Magnesium stearate
Ponceau 4R aluminium lake (E124)Cochinealred A (E124)
Sunset yellow FCF aluminium lake (E110)
Titanium dioxide (E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C

6.5 Nature and contents of container

Cartons of 30, 60 and 90 tablets in PVC/Aluminium blisters.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Les Laboratoires Servier
50, rue Carnot
92284 Suresnes Cedex
France

8 MARKETING AUTHORISATION NUMBER

PA0568/033/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 08 April 2007

10 DATE OF REVISION OF THE TEXT

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