

VASTAREL 20 mg

Film-coated tablet

INN : Trimetazidine

1. NAME OF THE MEDICINAL PRODUCT

VASTAREL 20 mg, film-coated tablet.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Trimetazidine dihydrochloride..... 20.00 mg

For one film-coated tablet.

Excipients with known effect: Sunset yellow FCF (E110) and cochineal red A (E124).

For the 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 route.

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 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.

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).

This medicinal product is generally not recommended during breast-feeding (see section 4.6).

Athletes: This medicinal product contains a drug substance that may give a positive result in anti-doping tests.

This medicinal product contains sunset yellow FCF (E110) and cochineal red A (E124) and may cause allergic reactions.

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. 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.

Breast-feeding

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 (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	Preferred Term
Nervous system disorders	Common	Dizziness, headache
	Uncommon	Paraesthesia
	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 disorders	Common	Rash, pruritus, urticaria
	Not known	Drug reaction with eosinophilia and systemic symptoms (DRESS), Acute generalised exanthematous pustulosis (AGEP) (see section 4.4), 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

4.9 Overdose

The information available concerning trimetazidine overdose is limited. 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 ion 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 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 1962-patient, three-month, randomised, double blind 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 1-mm ST depression and time to onset of 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 (+43.6 s versus +32.5 s placebo; $p=0.005$).

5.2 Pharmacokinetic properties

Absorption

- 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 approximately 55 ng.ml⁻¹.

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

Distribution

- 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%.

Elimination

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

Linearity

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

Special populations

Elderly subjects

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 (≥ 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. No safety concerns were observed in the elderly subjects as compared with the general population.

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

Maize starch, mannitol, povidone, magnesium stearate, talc.

Film-coating: Mixture of excipients for red coating 37771 FRG (titanium dioxide (E171), glycerol, sunset yellow FCF aluminium lake (E110), cochineal red A aluminium lake (E124), macrogol 6000, hypromellose, magnesium stearate), macrogol 6000.

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

In an aluminium container. Box of 60 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

Product Registration Holder:

Servier Malaysia Sdn Bhd
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