1. NAME OF THE MEDICINAL PRODUCT
VASTAREL MR, modified release film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Trimetazidine dihydrochloride (INN) 35 mg
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
The dose is one tablet of 35 mg of trimetazidine twice daily during meals.

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 <30 ml/min).

4.4 Special warnings and precautions for use
This medicinal product is generally not recommended during breastfeeding (see section 4.6).

This medicinal product is not a curative treatment for angina attacks, nor is it indicated as an initial treatment for unstable angina, nor myocardial infarction, nor in the pre-hospital phase nor during the first days of hospitalisation.

In the event of an angina attack, the coronaryopathy should be re-evaluated 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.
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
Not applicable.

4.6 Pregnancy and Breast-feeding

**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, it is preferable to avoid prescription during pregnancy.

**Breast-feeding**
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 has not shown 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, defined as adverse events considered at least possibly related to trimetazidine treatment are listed below using the following convention frequency: 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).

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>Preferred Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td>Common</td>
<td>Dizziness, headache</td>
</tr>
<tr>
<td>Parkinsonian symptoms (tremor, akinesia, hypotonia), gait instability, restless leg syndrome, other related movement disorders, usually reversible after treatment discontinuation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Rare</td>
<td>Palpitations, extrasystoles, tachycardia</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Rare</td>
<td>Arterial Hypotension, orthostatic hypotension that may be associated with malaise, dizziness or fall, in particular in patients taking antihypertensive treatment, flushing</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Common</td>
<td>Abdominal pain, diarrhoea, dyspepsia, nausea and vomiting</td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Common</td>
<td>Rash, pruritus, urticaria</td>
</tr>
<tr>
<td>Not known</td>
<td>Acute generalized exanthematous pustulosis (AGEP), angioedema</td>
<td></td>
</tr>
<tr>
<td>General disorders and administration conditions</td>
<td>Common</td>
<td>Asthenia</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Not known</td>
<td>Agranulocytosis, Thrombocytopenia</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Not known</td>
<td>Hepatitis</td>
</tr>
</tbody>
</table>

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
OTHER CARDIOVASCULAR ANTIANGINAL DRUG
Code ATC: 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 ensur-
ing the proper functioning of ionic pumps and trans-
membrane sodium-potassium flow whilst maintain-
ing 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,
ergy 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, trimetazi-
dine acts as a metabolic agent, preserving the myo-
cardial high-energy phosphate intracellular levels.
Anti-ischemic effects are achieved without concomi-
tant 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
when the benefit from other antianginal medicinal
products was insufficient.

In a 426-patients randomized, double blind, pla-
co-controlled study (TRIMPOL-II), trimetazi-
dine (60 mg/day) added to metoprolol 100 mg daily
(50 mg b.i.d) for 12 weeks significantly improved
exercise tests parameters and clinical symp-
toms as compared to placebo: total exercise dura-
tion +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, 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, place-
bo-controlled study (Sellier), one 35 mg trimetazi-
dine 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 place-
bo, 12 hours after taking the drug. A significant dif-
ference 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 sec-
ondary endpoints (total exercise duration, total work-
load and clinical endpoints).

In a 1962-patients three-month randomised, dou-
ble-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 symp-
tomatic patients, trimetazidine failed to demonstrate
a benefit on both ergometric (total exercise dura-
tion, time to onset of 1 mm ST segment depression
and time to onset angina) and clinical endpoints.
However, in the subgroup of symptomatic patients
(n= 1574) defined in a post-hoc analysis, trimetazi-
dine (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, maximum concentration
is observed, 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 60th hour, at the lat-
est.
- The pharmacokinetic characteristics of Vastarel
MR are not influenced by meals.
- The apparent distribution volume is 4.8 l/kg; 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 MR is on aver-
age of 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.
- A specific clinical study carried out in an elder-
ly population using a dosage of 2 tablets per day
taken in 2 doses, analysed by a kinetic population method, showed an increase in plasma exposure which does not justify a dosage modification.

5.3 Preclinical safety data
Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Calcium hydrogen phosphate dihydrate, hypromellose, povidone, anhydrous colloidal silica, magnesium stearate, macrogol 6000.
Film coating: titanium dioxide (E 171), 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 blister packs (PVC/Aluminium)
Not all pack sizes are necessarily marketed in all countries.

6.6 Special precautions for disposal
No special requirements for disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER
Les Laboratoires Servier
50, rue Carnot
92284 Suresnes Cedex
France

For any updates please refer to www.servier.com.
As the SmPC may vary from country to country please also refer to SERVIER’s local agents and/or distributors.