Annex III

Amendments to relevant sections of the summary of product characteristics and package leaflet

A. Summary of Products Characteristics

4.1 Therapeutic indications

[the currently approved indications should be deleted and replaced by the following]

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

[the wording below should be inserted]

The dose is one tablet of 20mg or 1 ml (20 drops) of oral drop solution of trimetazidine three times a day during meals.

The dose is one tablet of 35mg of trimetazidine twice daily 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 or 1 ml (20 drops) of oral drop solution twice daily, i.e., one in the morning and one in the evening during meals.

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 35mg in the morning during breakfast.

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 or 1 ml (20 drops) of oral drop solution 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).

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 35mg in the morning during breakfast.
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

[the currently approved contraindications should be deleted and replaced by the following]

- 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

[the wording below should be inserted]

[...]

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)

[...]

4.7 Effects on ability to drive and use machines

[the currently approved wording of this section should be deleted and replaced by the following]

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

[the wording below should be inserted]

[...]

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

[...]

5.1 Pharmacodynamic properties

[the wording below should be inserted]

[...]

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).

B. Package Leaflet

[the wording below should be inserted in the relevant sections]

1. What <invented name>is and what it is used for

This medicine is intended for use in adult patient, in combination with other medicines to treat angina pectoris (chest pain caused by coronary disease).

2. What you need to know before you take <invented name>

Do not take <invented name>
- if you are allergic to trimetazidine or any of the other ingredients of this medicine (listed in section 6),
- if you have a Parkinson disease: disease of the brain affecting movement (trembling, rigid posture, slow movements and a shuffling, unbalanced walk),
- if you have severe kidney problems.

Warnings and precautions

Talk to your doctor or pharmacist before taking <invented name>

[...]

This medicine can cause or worsen symptoms such as trembling, rigid posture, slow movements and a shuffling, unbalanced walk, especially in elderly patients, which should be investigated and reported to your doctor who could reassess the treatment.
[...]

Children and adolescents
<invented name> is not recommended in children aged below 18 years.

[...]

Pregnancy and breast-feeding
[...]

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
This medicine may make you feel dizzy and drowsy that may affect your ability to drive or use machinery.

3. How to take <invented name>

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose of <invented name> 20mg is one tablet to be taken three times a day during meals.

The recommended dose of <invented name> 20mg/ml solution is 20 drops to be taken three times a day during meals.

The recommended dose of <invented name> 35mg is one tablet to be taken two times a day during meals in the morning and evening.

If you have kidney problems or if you are older than 75 years old, your doctor may adjust the recommended dose.
[...]

4. Possible side effects

[...]
Common:
Dizziness, headache, abdominal pain, diarrhoea, indigestion, feeling sick, vomiting, rash, itching, hives and feeling of weakness.

Rare:
Fast or irregular heartbeats (also called palpitations), extra heartbeats, faster heartbeat, fall in blood pressure on standing-up which causes dizziness, light headiness or fainting, malaise (generally feeling unwell), dizziness, fall, flushing.

Not known:
Extrapyramidal symptoms (unusual movements, including trembling and shaking of the hands and fingers, twisting movements of the body, shuffling walk and stiffness of the arms and legs), usually reversible after treatment discontinuation.

Sleep disorders (difficulty in sleeping, drowsiness), constipation, serious generalised red skin rash with blistering, swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing.

Severe reduction in number of white blood cells which makes infections more likely, reduction in blood platelets, which increases risk of bleeding or bruising.
A liver disease (nausea, vomiting, loss of appetite, feeling generally unwell, fever, itching, yellowing of the skin and eyes, light coloured bowel motions, dark coloured urine).

If you get any side effects, talk to your doctor or pharmacist. This includes any side effects not listed in this leaflet.