

Annex II

Scientific conclusions and grounds for variation to the terms of the Marketing Authorisations

Scientific conclusions

Overall summary of the scientific evaluation of trimetazidine containing medicinal products

(see Annex I)

Trimetazidine (TMZ) is a metabolic agent whose aim is to protect against ischemia by increasing glucose metabolism relative to that of fatty acids. Its mechanism of action results partly of its effect on cellular metabolism. By decreasing fatty acid oxidation at the level of 3-ketoacyl coenzyme A thiolase, it favours glucose oxidation, which improves the use of the cells' energy reserves in the event of ischaemia. Trimetazidine has no hemodynamic effect on blood pressure or heart rate.

Trimetazidine-containing medicinal products are indicated for prophylactic treatment of angina pectoris crisis, ancillary symptomatic treatment of vertigo and tinnitus and ancillary treatment of visual acuity decrease and visual field disturbances due to vascular reasons.

Trimetazidine medicinal products have been authorised in 21 European Member states. They were first authorised in France in 1978 and are available in three different pharmaceutical forms in the EU: 20 mg tablet, 20 mg/ml oral solution and 35 mg modified release (MR) tablet.

France on 22 April 2011 requested the CHMP to give its opinion under Article 31 of Directive 2001/83/EC on whether the marketing authorisation for trimetazidine-containing medicinal products should be maintained, varied, suspended or withdrawn on the basis of the increased Parkinson's reports.

Of note, all the data submitted and assessed for this referral are newly available data since the first authorisation of trimetazidine.

EFFICACY

Angina pectoris

The clinical experience with trimetazidine dates back to the early 70s.

The CHMP considered all the studies submitted for this indication. However, the TRIMPOL-II study (2001), the study by Sellier (2003) and the revised data from the VASCO study (2011) were the studies providing evidence generated in support of the add-on indication of trimetazidine in symptomatic patients with angina pectoris. These data support the efficacy of trimetazidine in add-on to beta-blockers. In addition the two studies by Manchanda (1997 and 2003) and four other minor studies are considered supportive of the efficacy of trimetazidine in add-on to calcium channel blockers (CCBs).

In a 426-patients randomised, 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.

The TRIMPOL-II showed that trimetazidine significantly improves exercise capacity and exercise-induced myocardial ischemia when added to metoprolol. It should be noted that the study was conducted using the Bruce protocol that it is known to underestimate the treatment effect of drugs compared to the modified Bruce protocol. The study results may thus be considered conservative in terms of magnitude of the effect of trimetazidine. Although the methodology followed by the MAH may be regarded as not totally compliant to the currently accepted standards, no major bias affecting the

interpretation of study results appears evident and all analyses show a beneficial effect of trimetazidine combined with metoprolol on exercise tolerance, myocardial ischemia and clinical symptoms. The post-hoc analysis of the study in 298 patients receiving trimetazidine in combination mainly with metoprolol is in line and it is considered useful to better assess the effect of trimetazidine in a population of patients that are often difficult to be treated with haemodynamic agents. Of importance the efficacy was confirmed in patients at maximal dose of metoprolol as well as in patients with recurrent angina.

The aim of the Sellier study (2003) was to assess the efficacy of the combination of trimetazidine MR 70 mg/day in patients suffering from angina pectoris who were insufficiently controlled on 50 mg/day of atenolol after two months of treatment. 223 patients were randomized for this double blind, placebo-controlled study where one 35 mg trimetazidine modified release tablet (b.i.d.) was added to 50 mg atenolol (o.d.) for 8 weeks and 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 order to show a benefit on daily episodes of angina it is important to adequately assess the baseline occurrence of angina and sublingual nitrate use and to calculate the sample size on the basis of the expected treatment effect. The Sellier study was an exercise study not primarily designed to assess clinical parameters. It is considered that the study is only adequate to show the efficacy of trimetazidine with reference to the primary endpoint, time to onset of angina pectoris, as 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, 2011) 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 ($n=1574$) 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; $p=0.005$).

The VASCO study was conducted in symptomatic and asymptomatic patients with chronic ischemic heart disease. Less than 50% of patients included in the VASCO study had chronic stable angina despite probable coronary artery disease. The presence of stable angina pectoris is a pivotal inclusion criterion as it identifies the target population for the use of anti-anginal drugs. Indeed, it is well known that patients with proven coronary artery disease who are asymptomatic may not have inducible ischemia and that in these patients anti-anginal treatments are ineffective in improving exercise capacity.

The VASCO study showed a significant difference in the effect on ergometric parameters between trimetazidine at the highest dosage (140 mg) and placebo in the group of symptomatic patients. The analysis performed by the MAH has been repeated independently by the Italian Institutes of Health (ISS). This analysis showed that in patients with chronic stable angina trimetazidine given as add-on to atenolol significantly improved exercise tolerance ($p<0.01$), time to 1 mm ST segment depression and time to angina. The improvement in the primary end point with trimetazidine was observed in the pooled analysis of patients receiving 35 and 70 mg twice daily and in the analysis of patients receiving either 35 mg twice daily or 70 mg twice daily.

The efficacy of trimetazidine was also summarised in a recent network meta-analysis including 358 clinical trials and 27058 patients. Trimetazidine was shown to have an effect very similar to that of non-heart rate-lowering anti-anginal agents: nicorandil, ranolazine, long-acting nitrates and

dihydropyridines, with less than a few seconds differences in exercise tolerance test (ETT) ergometric parameters. The efficacy of trimetazidine is sufficiently demonstrated as add-on therapy in the short-medium-term (weeks /months) treatment of symptomatic patients with angina who are inadequately controlled by or intolerant to first-line antianginal therapies.

The CHMP considers that the revised indication is in line with the scientific evidence available at present for trimetazidine as add-on therapy and it is supported by trials that became available after the initial authorisation and considered to be of sufficient methodological quality and by meta-analyses that have come to similar conclusions. Recent surveys in patients with coronary artery disease have shown that most patients with angina do not receive adequate anti-anginal therapy because of haemodynamic intolerance or chronotropic incompetence. Therefore, trimetazidine as add-on therapy may represent an optional treatment drug to be used in association with first-line anti-anginal drugs especially in those patients for whom optimally control of symptoms cannot be achieved with other anti-anginal drugs in monotherapy due to haemodynamic intolerance or chronotropic incompetence.

Otology - Ear, Nose and Throat (ENT)

In response to the CHMP request regarding the re-evaluation of the risk/benefit ratio of trimetazidine (all forms and dosages) in the ENT indications, 9 clinical studies (Wayoff, 1984; Sterkers, 2001; Vitte, 2002; Haguenaer, 1980; Kluyskens, 1990; Martini, 1990; Morgon 1990; Coyas 1990 and France cochlea study, 2009 presented as support of safety since the efficacy objective was not reached) were submitted or presented as literature references. Most of these studies included patients presenting very heterogeneous pathologies of various severities with absence of prior stratification on these pathologies, and of very limited duration of treatment (between 2 and 3 months) not in line with what is required by these pathologies that necessitate long term treatments.

Among these studies, five studies were conducted against placebo including the additional study published in 1990 by Coyas. Each study generally included multiple objectives (pharmacodynamic or clinical evaluations). They also mixed ENT pathologies and symptomatology from different etiologies such as tinnitus, different kinds of vertigo or deafness. The main studies conducted versus placebo were Wayoff study (tinnitus, dizziness, hearing loss) and Morgon study (tinnitus). They are studies whereby the results, often presented as statistically in favour of trimetazidine, are disputable mainly for methodological reasons. Two additional and more recent studies were focused on dizziness but the exploratory nature of the Sterkers study (2001) and the extremely small populations included (28 patients) do not make it possible to give any demonstrative weight to the results reported. In addition, Vitte study (2002) had the same methodological weaknesses as the Wayoff and Morgon studies. Favourable results from 'Dizziness Handicap Inventory questionnaire' were suggested by the small Sterckers and Vitte studies. These results were pooled without confirming the beneficial effect. Three studies were conducted against betahistine (Haguenaer, 1980; Kluyskens, 1990; Martini, 1990) to demonstrate a clinical benefit of trimetazidine in the treatment of dizziness. None of these three studies was predefined as non-inferiority study. Therefore, the results which were presented as supporting a similar efficacy than trimetazidine are not reliable. Thus, all of these elements deriving from post-approval data do not demonstrate a relevant clinical benefit of trimetazidine for patients suffering from tinnitus, dizziness or hearing loss.

In conclusion, the data submitted for trimetazidine with respect to ENT indications, insufficiently support the demonstration of a relevant clinical benefit for these patients suffering from tinnitus, vertigo or hearing loss symptomatology who were targeted by the ENT therapeutic indications as mentioned currently in the European marketing authorisations. The studies suggested limited methodology in the ENT field and do not confirm the current methodology of investigation by applying

the basic statistical principles of clinical trials methodology. Of the ten studies submitted, nine do not apply the relevant methodological principles currently required to demonstrate efficacy. Therefore, considering these methodological weaknesses, the dossier is insufficient to conclude that trimetazidine has satisfactorily demonstrated a clinical benefit as adjuvant symptomatic treatment of dizziness, tinnitus or hearing loss.

The CHMP concluded that the limited data generated by the clinical trials submitted for the ENT indication, insufficiently support the demonstration of a relevant clinical benefit of trimetazidine for patients suffering from tinnitus, vertigo or hearing loss and that either the currently ENT registered indication or the newly claimed indications cannot be supported.

Ophthalmology

In response to the CHMP's request regarding the re-evaluation of the risk/benefit ratio of trimetazidine (all forms and dosages) in its ophthalmologic indications, the clinical package submitted comprises of nine studies. Eight of them show inclusions of patients presenting very heterogeneous pathologies of various severities with absence of prior stratification on these pathologies, and short durations of treatment (between 2 and 6 months) while these pathologies are known to progress slowly and to require extended treatments. These pathologies lead ultimately to blindness. Most ophthalmologic trimetazidine clinical trials have been conducted with the 20 mg strength but in some studies the daily doses used (20mg and 40 mg/day) were lower than those recommended in the current marketing authorisation (60 mg or 70 mg), which is also a limit of these studies, particularly in documenting the safety at the registered dosage.

Among these nine studies, three were non-comparative studies (Guillaumat, 1982; Millara, 1988; Nowak, 2007); three were comparative studies of short duration (up to 3 months) conducted against products used at the time of these studies e.g. cinnarizine, piridoxilate which are no more considered as therapies of choice to treat or prevent retinal or glaucoma diseases by the ophthalmologists; two studies were conducted against placebo (Couderc, 1984 and Aron-Rosa, 1988). Finally, the most recent study using an appropriate methodology was submitted only for safety purpose as the efficacy objective was not reached (France ARMD 2, 2008).

The clinical studies supporting ophthalmic field suffer from major methodological flaws.

The non-comparative nature of three studies conducted in patients with heterogeneous ocular disorders, did not allow concluding to the existence of a clinical benefit.

The three studies of short duration (up to 3 months) conducted against reference products of the time (e.g cinnarizine, piridoxilate), included a small number of patients who presented very heterogeneous or poorly defined pathologies (n=19, n=24 and n=8 respectively for the Cornand (1982), Cordella (1982) and Perdriel (1988) studies). Furthermore, these studies present other specific weaknesses: the Cordella study (versus cinnarizine) did not include inter-group comparison. Furthermore, the multiplicity of comparisons was not taken into account in the statistical analyses and the criteria were not presented hierarchically, so this comparison cannot have any demonstrative value; and lastly, the Perdriel single dose electroretinographic study (versus pyridoxilate) used an injectable intravenous form of trimetazidine 20 mg that has not been authorised.

The most recent study conducted with trimetazidine 35 mg from 1999 (France, ARMD 2) related to a higher number of patients monitored for 3 to 5 years. Results from this study did not highlight any clinical benefit of trimetazidine in comparison to the placebo to prevent the bilateralisation of choroidal neovascularisation in patients suffering from age-related macular degeneration, principal criterion of

evaluation chosen to demonstrate the clinical benefit of trimetazidine 35 mg to slow the progression of age-related macular degeneration (ARMD).

Based on the data submitted for the ophthalmologic indications, the CHMP considered that the evidence does not fulfill the requirements and criteria for the evaluation of efficacy currently requested in these pathologies. The submitted data comparing TMZ to either placebo or the other reference products or based on cohorts without comparator provide insufficient demonstration of a relevant clinical benefit of trimetazidine in the ancillary treatment of visual acuity decrease and visual field disturbances due to vascular reasons. The CHMP concluded that following the assessment of all these studies the efficacy of trimetazidine is not proven on the ophthalmological indication.

SAFETY

A prescription study in France showed that trimetazidine was prescribed in patients in cardiovascular indications in 45.3% of cases, in ENT indications in 30% of cases and in ophthalmological indications in 0.4% of cases. In 24.3% of cases, the indication was unknown. Patients with a cardiovascular profile were significantly older (mean age: 74.8 years) than those with an ophthalmological and ENT profile (70.3 years and 63.5 years, respectively).

The main identified serious ADR is related to Parkinson syndrome and related symptoms. This risk has been identified in post marketing setting and in literature based on: positive dechallenge of Parkinson symptoms after the only withdrawal of TMZ, positive rechallenge, significant higher coprescription of antiparkinson drugs in TMZ group compared to control group (IMS study) and significant higher number of patients that begin antiparkinson drugs after the introduction of TMZ compared to control group (IMS study).

The most exposed population based on sales data, is patients aged more than 75 years old, and they received the treatment for very long periods mainly in cardiology indications.

The reporting rate of Parkinson's syndrome plausibly related to trimetazidine is stable over time since the last 8 years, despite the increase, since 2007, in the number of spontaneous reports of Parkinson's syndrome and related symptoms.

It is acknowledged that extrapyramidal symptoms reported in patients receiving TMZ have a low prevalence (incidence of 0.36/100,000 PY) and are generally reversible after TMZ withdrawal. However, some patients had symptoms only partially reversible after TMZ withdrawal, and the connection to TMZ in some cases of non-reversible symptoms cannot be ruled out.

Considering all currently available data, the CHMP concluded that trimetazidine-containing medicines should be contraindicated in patients with Parkinson disease, parkinsonian symptoms, tremors, restless leg syndrome, and other related movement disorders. In addition, the SmPC has to be amended to include a warning about trimetazidine induced parkinsonism, its diagnosis and management. These changes are considered adequate to manage the risk of parkinsonian symptoms and tremors.

Elderly patients may have increased trimetazidine exposure due to age-related decrease in renal function. Population pharmacokinetics data indicate that serious adverse events were more frequent in treated elderly patients with high trimetazidine plasma concentrations. The Emeriau PK study has shown high plasma concentrations of trimetazidine in old patients, receiving the usual dose of 35 mg twice daily. Accordingly, the SmPC has been amended to include dose information in the elderly and in patients with moderate renal impairment (creatinine clearance [30-60] ml/min). In addition, a pharmacokinetics study was agreed with the MAH to investigate the effects of renal impairment and age on the trimetazidine safety profile.

Considering all currently available data, the CHMP concluded that trimetazidine-containing medicinal products should be contraindicated in patients with severe renal impairment (creatinine clearance < 30ml/min).

Some new potential, very rare and reversible adverse effects were highlighted during the referral procedure, including thrombocytopenia, agranulocytosis and liver dysfunction and have been included in the risk management plan (RMP) and reflected in the relative sections of the SmPC.

The proposed multicentre, randomised, double-blind, placebo controlled long-term study in post-percutaneous coronary intervention (PCI) patients and the prospective and comparative cohort study to assess the prevalence of EPS in patients receiving trimetazidine may be adequate to solve the concerns on long-term efficacy and safety of trimetazidine.

A PASS study to address all important, potential and identified risks, particularly Parkinsonism, and a Drug utilization study to monitor whether the risk minimization measures put in place as results of the referral procedure are effective have been requested by the CHMP.

Overall conclusion

Overall, the CHMP concluded that after assessing the newly available data, the benefits continue to outweigh the risks in patients with angina pectoris but that treatment should be restricted to add-on to existing treatments in patients who are not adequately controlled by or intolerant to other medicines for angina pectoris. The new proposed wording in the angina pectoris indication is in accordance with the available efficacy and safety data assessed. For the remaining two indications of symptomatic treatment of tinnitus, vertigo and of visual field disturbances, the CHMP concluded that in view of the newly available safety data and very limited efficacy, the benefits no longer outweigh the risks under normal conditions of use and therefore these therapeutic indications should be removed.

In patients with moderate renal impairment (creatinine clearance [30-60] ml/min) the recommended dose has been added in the SmPC. Elderly patients may have increased trimetazidine exposure due to age-related decrease in renal function. Dose titration in elderly patients should be exercised with caution. Considering all the currently available data the CHMP concluded that the trimetazidine should be contraindicated in patients with Parkinson disease, parkinsonian symptoms, tremors, restless leg syndrome, and other related movement disorders as well as in patients with severe renal impairment (creatinine clearance < 30ml/min).

The CHMP agreed that 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 prevalence and are usually reversible after treatment discontinuation. The majority of the patients who recovered, had their symptoms disappeared within four months after trimetazidine withdrawal. If parkinsonian symptoms persist more than four months after drug discontinuation, a neurologist opinion should be sought. Caution should be exercised when prescribing trimetazidine to patients in whom an increased exposure is expected moderate due to renal impairment, or in elderly patients older than 75 years old.

The CHMP endorsed a communication, Direct Healthcare Professional Communication (DHPC), to communicate the outcome of the present review.

The CHMP also agreed on a study protocol to assess the effect of renal impairment and age on trimetazidine pharmacokinetics for the study to be conducted. A Post-Authorisation Safety Study (PASS

study) to address all important, potential and identified risks, particularly Parkinsonism and a drug utilization study to verify the compliance of prescribers regarding the restricted indication after marketing authorisation changes was also agreed.

Benefit –risk balance

Therefore, the Committee concluded that the benefit-risk balance of trimetazidine- containing medicinal products in the 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, remains positive under normal conditions of use, subject to the restrictions, warnings, changes to the product information, additional pharmacovigilance activities and risk minimisation measures agreed. For the remaining two indications of symptomatic treatment of tinnitus, vertigo and of visual field disturbances, the CHMP concluded that in view of the newly available safety data and very limited efficacy, the benefits no longer outweigh the risks under normal conditions of use and therefore these therapeutic indications should be removed.

Grounds for the variation to the terms of the marketing authorisation

Whereas

- The Committee considered the referral under Article 31 of Directive 2001/83/EC;
- The Committee reviewed all available submitted data from clinical studies, published literature and post-marketing experience on the safety of trimetazidine containing medicinal products, in particular with regards to the Parkinson syndrome and related events. The Committee concluded that trimetazidine is associated with the occurrence of Parkinson syndrome and related symptoms.
- The Committee also considered the cumulative efficacy and safety data submitted for the indications of the prophylactic treatment of attacks of angina pectoris, ancillary symptomatic treatment of vertigo and tinnitus and ancillary treatment of visual acuity decrease and visual field disturbances due to vascular reasons.
- The Committee is of the opinion that the benefits continue to outweigh the risks in patients with angina pectoris but that treatment should be restricted to add-on to existing treatments in patients who are not adequately controlled by or intolerant to other medicines for angina pectoris.
- For the indications of symptomatic treatment of tinnitus, vertigo and of visual field disturbances, the CHMP concluded that in view of the newly available safety data and very limited efficacy, the benefits no longer outweigh the risks under normal conditions of use and therefore these therapeutic indications should be removed.
- Considering all the currently available safety data the Committee concluded that trimetazidine should be contraindicated in patients with Parkinson disease, parkinsonian symptoms, tremors, restless leg syndrome, and other related movement disorders as well as in patients with severe renal impairment (creatinine clearance < 30ml/min).
- The Committee also recommended that trimetazidine can cause or worsen parkinsonian symptoms (tremor, akinesia, hypertonia). 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 prevalence and are usually reversible after treatment discontinuation. Caution should be exercised when prescribing

trimetazidine to patients in whom an increased exposure is expected such as with moderate renal impairment and elderly patients older than 75 years old.

The Committee, therefore, concluded that the benefit-risk balance of trimetazidine- containing medicinal products remains positive under normal conditions of use, subject to the restrictions, warnings, changes to the product information, additional pharmacovigilance activities and risk minimisation measures agreed, only as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled by or intolerant to first-line anti-anginal therapies.