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Assessment Report for trimetazidine containing medicinal products

Procedure number: EMEA/H/A-31/1305

Referral under Article 31 of Directive 2001/83/EC

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

1. Background information on the procedure

1.1. Referral of the matter to the CHMP

On 22 April 2011, France triggered a referral under Article 31 of Directive 2001/83/EC, as amended. The CHMP was requested to give its opinion on whether the marketing authorisations for trimetazidine containing medicinal products should be maintained, varied, suspended or withdrawn.

The procedure described in Article 32 of Directive 2001/83/EC, was applicable.

2. Scientific discussion

2.1. Introduction

Trimetazidine [1-(2,3,4 trimethoxy benzyl)-piperazine dihydrochloride] (TMZ), a metabolic agent, protects against ischemia by increasing glucose metabolism relative to that of fatty acids.

The mechanism of action of trimetazidine has not been totally elucidated in humans; it should be partly a result of its effect on cellular metabolism. Briefly, by decreasing fatty acid oxidation at the level of 3-ketoacyl CoA thiolase (*Kantor et al., 2000*), it should favour 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 were first authorised in Europe in France in 1978. Three pharmaceutical forms are available in EU: 20 mg tablet, 20 mg/ml oral solution and 35 mg modified release (MR) tablet.

Trimetazidine-containing medicinal products are indicated in EU for the treatment of:

i) prophylactic treatment of angina pectoris crisis ;

ii) ancillary symptomatic treatment of vertigo and tinnitus and

iii) ancillary treatment of visual acuity decrease and visual field disturbances due to vascular reasons.

In France, a benefit/risk ratio reassessment of trimetazidine- containing products was triggered in 2009, motivated by non-conclusive results of the VASCO clinical study in the indication of stable angina and the conclusions of several pharmacovigilance investigations since 2005 that pointed out some concerns on tolerance.

Regarding the clinical efficacy of trimetazidine (TMZ) for all authorised indications, the majority of the studies have been conducted with the 20 mg dosage. However, most of all these trials although completed after the initial authorization of the products, are rather old; either carried out versus placebo or active comparator with general methodological level that are considered low compared to today's standards.

For the angina pectoris indication, the VASCO study was requested by France to further confirm the benefits of trimetazidine 35 mg MR in this target population. After review of overall results of the VASCO study and other studies in *the prophylactic treatment of angina pectoris crisis*, the French national authority concluded that the efficacy of trimetazidine still remained under concern in this indication.

For the other two indications, the treatment of ancillary symptomatic treatment of vertigo and tinnitus and ancillary treatment of visual acuity decrease and visual field disturbances due to vascular reasons,

the French assessment concluded that the clinical data did not demonstrate the efficacy of TMZ in these indications.

Regarding the safety profile of TMZ, the French National enquiries have led in particular to restrict the status of prescription in France (from OTC to Prescription only medicine) and to reinforce the Summary of Product Characteristics (SmPC).

Following data from the Pharmacovigilance database and from the PSUR of trimetazidine containing products, from February 2008 to January 2011, 48 cases (of which 45 in France) of Parkinson syndrome and other motor disorders such as tremor, muscle rigidity and walking disorders, and restless legs syndrome were reported. This syndrome almost always occurred in patients without prior known Parkinson disorder. The outcome was often favourable after trimetazidine discontinuation even after months or years of evolution. Thus, the major issue related to trimetazidine containing medicinal products concerns neurological side effects. Trimetazidine is a piperazine derivative the mechanism of action of which remains unclear. These piperazine derivatives may have action on dopaminergic neurons due to their chemical structure.

In April 2011, following the evaluation of the benefit/risk balance of trimetazidine, the French National Authorities gave a negative opinion on the benefit/risk ratio of trimetazidine-containing medicinal for all authorised indications and for all dosages.

Based on the above and taking into account that trimetazidine containing medicinal products are also authorised in other member states, the French NCA considered of community interest to have a review of the overall risk-benefit balance of trimetazidine medicinal containing products in all currently authorised indications at European level. Therefore, this issue was referred to the CHMP under Article 31 of Directive 2001/83/EC.

France has 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.

2.2. Clinical efficacy

The MAHs have provided information on studies and on published data available. Of note, the data submitted and assessed during this procedure became available after the granting of the initial Marketing Authorisation, including some recent data.

In this report the efficacy information for the three authorised indications of trimetazidine will be discussed separately.

2.2.1 Angina Pectoris

Current recommendations for the management of stable angina from European Society of Cardiology (ESC) advise medical treatment with anti-anginal agents in combination with strategies to reduce adverse clinical outcomes related to risk factors, such as smoking cessation, physical activity, daily aspirin, and treatment of dyslipidaemias, hypertension, and diabetes that increase the risk of progression of coronary disease (*Fox et al., 2006*). The goals of the pharmacological treatment of stable angina pectoris are to improve quality of life by reducing the severity and/or frequency of symptoms and to improve prognosis, the latter being achieved by aspirin, statin, and angiotensin-converting enzyme (ACE) inhibitor therapy. Pharmacological treatment aimed at improving symptoms and/or reducing ischemia includes: beta-blockers (recommended as first-line therapy), calcium channel blockers (CCBs), long-acting nitrates, nicorandil, molsidomine and trimetazidine. Metabolic agents may be used where available as add-on therapy or substitution therapy when conventional drugs are not tolerated (class IIb, level of evidence B).

The clinical development program of trimetazidine in stable angina pectoris is presented in the Table 1 below.

Table 1: General presentation of the clinical studies in angina pectoris

Identification	Description of the study	Group	Treatment Duration	Assessment Criteria
PROSPECTIVE STUDIES				
A. Dose-response study (n=1)				
CANICAVE Canicave, 1980	Phase II SB vs Pbo	N=27 -TMZ 10, 20, 40, 60 mg (n=27)	4 x 2 weeks	-Clinical criteria -Exercise capacity
B. Acute haemodynamic effect (n=2)				
SELLIER Sellier et al., 1987	Phase II R, DB, CO, Pbo-C	2 groups (N=10) -Placebo/TMZ (n=5) -TMZ/Placebo (n=5)	Single dose	-Exercise capacity
PORNIN Pornin et al., 1994	Phase II R, DB, 3 PG, Pbo-C	3 groups (N=15) -Placebo (n=5) -TMZ 1 mg.kg-1 (n=5) -TMZ 1.5 mg.kg-1 (n=5)	IV bolus	-Haemodynamic parameters
C. Studies conducted in Monotherapy Controlled studies versus placebo (n=4)				
PASSERON Passeron, 1986	Phase III R, DB, 2 PG, Pbo-C	2 groups (N=54) -Placebo (n=27) -TMZ 60 mg/d (n=27)	2 weeks	-Clinical criteria -Exercise capacity
SELLIER Sellier, 1986	Phase III R, DB, 2 PG, Pbo-C, MC	2 groups (N=32) -Placebo (n=14) -TMZ 60 mg/d (n=18)	4 weeks	-Exercise capacity -Clinical criteria
PRASAD Prasad, 1989	Phase III R, DB, 2PG, Pbo-C	2 groups (N=40) -Placebo (n=20) -TMZ 60 mg/d (n=20)	2 weeks	-Exercise capacity -Clinical criteria
CHIERCHIA Lu, 1998	Phase III R, DB, CO, Pbo-C	2 groups (N=15)	2 weeks	-Basal cardiac function -LV function
D. Studies conducted in Monotherapy Controlled studies versus reference agent (n=4)				
Versus Calcium channel blockers				
GROSGOGEAT Grosgogeat, 1987	Phase III R, DB, CO, CR	2 groups (N=26) -TMZ/Prenylamine (n=12) -Prenylamine/TMZ (n=14)	2x30 days	-Clinical criteria
DALLA-VOLTA Dalla-Volta et al., 1990	Phase III R, DB, CO, CR	2 groups (N=39) -NIF/TMZ (n=19) -TMZ/NIF (n=20)	2x6 weeks	-Clinical criteria -Exercise capacity
KOYLAN Koylan et al. 2004	Phase III, R, DB, 2PG, CR, MC	2 groups (N=116) -TMZ (n=58) -DIL (n=58)	4 weeks	-Exercise capacity -Clinical criteria -Holter-ECG
Versus beta-blockers				
DETRY Detry et al., 1994	Phase III R, DB, 2 PG, CR, MC	2 groups (N=149) -TMZ (n=71) -PRO (n=78)	12 weeks	-Exercise capacity -Clinical criteria
E. Studies conducted in Combination to other anti-anginal agent				
Controlled studies versus placebo (n=11)				
In combination with calcium channel blockers				
SCHUTZ Schutz, 1984	Phase III R, DB, 2PG, Pbo-C, MC	2 groups (N=15) -NIF+TMZ (n=7) -NIF + Placebo (n=8)	15 days	-Exercise capacity -Clinical criteria
BROCHIER Brochier et al., 1986	Phase III R, DB, 2 PG, Pbo-C	2 groups (N=29) -NIF+TMZ (n=14) -NIF+Placebo (n=15)	2 weeks	-Clinical criteria
LEVY Levy et al., 1995	Phase III R, DB, 2 PG, Pbo-C, MC	2 groups (N=67) -DIL+TMZ (n=32) -DIL+Placebo (n=35)	6 months	-Exercise capacity
BERMUDEZ Bermudez, 1995	Phase III R, DB, 4PG, Pbo-C	4 groups (N=51) -DIL+TMZ (n=17) -DIL+Placebo (n=17) -TMZ (n=9) -Placebo (n=8)	3 months	-Exercise capacity -Clinical criteria -Holter-ECG
AKSOYEK Aksoyek, 1996	Phase III R, DB, 2PG, Pbo-C	2 groups (N=21) -TMZ+DIL+ISMN (n=11) -Placebo+DIL+ISMN	2 weeks	-Exercise capacity -Clinical criteria

MANCHANDA Manchanda, 1997	Phase III R, DB, 2 PG, Pbo-C, MC	2 groups (N=64) -DIL+TMZ (n=32) -DIL+Placebo (n=32)	4 weeks	-Exercise capacity -Clinical criteria
MANCHANDA Manchanda, 2003	Phase III R, DB, 2 PG, Pbo-C	2 groups (N=50) -DIL+TMZ (n=25) -DIL+Placebo (n=25)	4 weeks	-Clinical criteria -Exercise
In combination with beta-blockers				
DENG Deng et al., 2002	Phase III R, DB, 2PG, Pbo-C,	2 groups (N=94) -MTP+TMZ (n=48) -MTP+Placebo (n=46)	4 weeks	-Clinical criteria
TRIMPOL II, Szwed et al., 2001	Phase IV R, DB, 2PG, Pbo-C, MC	2 groups (N=426) -MTP+TMZ (n=211) -MTP+Placebo (n=215)	12 weeks	-Exercise capacity -Clinical criteria
SELLIER Sellier 2003	Phase III R, DB, 2PG, Pbo-C, MC	2 groups (N=223) -ATE+TMZ (n=117) -ATE+Placebo (n=106)	8 weeks	-Exercise capacity -Clinical criteria
VASCO 2011 Report [NP25601]	Phase III R, DB, 3PG, Pbo-C, MC	3 groups (N=1962) -ATE+TMZ 70 mg (n=654) -ATE+TMZ 140 mg (n=655) -ATE+Placebo (n=653)	12 weeks	-Exercise capacity -Clinical criteria
Controlled studies in combination with beta-blocker versus nitrates (n=3)				
TOUTOUZAS Michaelides et al., 1997	Phase III R, DB, 2 PG, CR, MC	2 groups (N=53) -PRO + TMZ (n=26) -PRO + ISDN (n=27)	8 weeks	-Clinical criteria -Exercise capacity
HANANIA Hanania, 2002	Phase III R, DB, 2PG, CR, MC	2 groups (N=185) -ATE+TMZ (n=93) -ATE+ISMN (n=92)	8 weeks	-Exercise capacity -Clinical criteria
OGANOV Oganov, 2007	Phase III R, SB, 2PG, CR, MC	2 groups (N=903) -BB+TMZ (n=456) -BB+ISDN (n=447)	12 weeks	-Clinical criteria -Quality of life
In combination with usual therapy				
SHLYAKHTO Shlyakhto, 2002	Phase III R, SB, 2PG, Pbo-C	2 groups (N=40) -ST+TMZ (n=20) -ST+ Placebo (n=20)	4 weeks	-Exercise capacity -Clinical criteria
CHAZOV Chazov, 2005	Phase III R, SB, 2PG, Pbo-C, MC	2 groups (N=177) -ST+TMZ (n=90) - ST+Placebo (n=87)	12 weeks	-Exercise capacity -Clinical criteria
F. TMZ in specific clinical situations				
Elderly				
TRIMPOL 1 Szwed 1997	Phase IV O, C	N=700 -ST=TMZ	4 weeks	-Exercise capacity -Clinical criteria
TRIMPOL 1 elderly Szwed, 1997	Elderly Phase IV O, MC	1 subgroup (N=71/700)) - ST+TMZ	4 weeks	-Exercise capacity -Clinical criteria
KÖLBEL Kölbel, 2003	Elderly Phase IV O, MC	N=120 -ST+TMZ	12 weeks	-Exercise capacity -Clinical criteria
MARAZZI Marazzi, 2009	Elderly Phase III R, DB, 2PG, Pbo-C, MC	2 groups (N=47) -ST+TMZ (n=23) -ST+Placebo (n=24)	6 months	-Clinical criteria -Quality of life
Diabetics patients				
TRIMPOL 1 diabetics Szwed, 1999	Diabetics Phase IV, O, MC	1 subgroup (N=50/700) -ST+TMZ	4 weeks	-Exercise capacity -Clinical criteria
DIETRIC Padial, 2005	Diabetics Phase IV O, MC	N=580 -ST+TMZ	6 months	-Exercise capacity -Clinical criteria
RIBEIRO Ribeiro, 2007	Diabetics Phase III R, DB, CO, Pbo-C	2 groups (N=10) - TMZ/Placebo (n=5) - Placebo/TMZ (n=5)	6 weeks	-Exercise capacity -Clinical criteria
MARAZZI Marazzi, 2007	Diabetics Phase III R, DB, 2PG, Pbo-C	2 groups (N=30) -TMZ (n=15) -Placebo (n=15)	6 months	-Clinical criteria -Holter ECG
G. Other fields of investigation				
Peripheral artery disease				
BUZIN Buzin, 2007	Phase III R, SB, 2PG	2 groups (N=68) -TMZ (n=38) -control (n=30)	6 months	-Treadmill testing -Ankle-brachial index -Biological markers
VITALE Vitale, 2011	Phase III R, DB, 2PG, Pbo-C	2 groups (N=100) -TMZ (n=50) -Placebo (n=50)	3 months	-Treadmill testing -Ankle-brachial index

Severe Heart Failure				
BROTTIER Brottier, 1990	Phase III R, DB, 2PG, Pbo-C	2 groups (N=20) -TMZ (n=9) -Placebo (n=11)	6 months	-Clinical (NYHA) -Echo -Radionuclide ventriculography
VITALE Vitale, 2004	Phase III R, DB, 2PG, Pbo-C	2 groups (N=44) -TMZ (=25) -control (n=19)	6 months	-Clinical criteria -Quality of life -Echo
FRAGASSO Fragasso, 2011	Phase III R, SB, 2PG	2 groups (N=47) -TMZ (=23) -Placebo (n=24)	3 months	-Clinical (NYHA) -Quality of life -Echo
Assessment of quality of life				
TRIUMPH Malkolkin, 2004	Phase IV O, MC	N= 906 -ST+TMZ	8 weeks	-Clinical criteria -Quality of life
TRIADA Chaloupka, 2006	Phase IV O, MC	N= 74 -ST+TMZ	12 weeks	-Exercise testing -Clinical criteria -Quality of life
RETROSPECTIVE STUDY				
METRO Iyengar, 2009	RC, MC	N=353		-post-MI mortality (GRACE score)
META-ANALYSIS				
A. Anginal pectoris				
Cochrane review Ciaponni 2005		N=1378		-Clinical criteria - ST segment depression
Network meta-analysis 2011		N=27058		-Clinical criteria -Exercise capacity
B. Left ventricular dysfunction				
Gutierrez 2006		N=214		- Effects on left ventricular function
Hu 2011		N=545		- Effects on left ventricular function
Gao 2011		N=955		- Effects on left ventricular function

ATE, atenolol; BB, beta-blockers; CO, cross-over; CR, controlled vs reference agent; DB, double-blind; DIL, diltiazem; IV; intravenous; LV; left ventricular; ISDN, isosorbide dinitrate; ISMN, isosorbide mononitrate; MC, multicentre; MTP, metoprolol; NIF, nifedipine; O, open; Pbo-C, placebo-controlled; PG, parallel group; PRO, propranolol; R, randomised; RC, retrospective cohort; SB, single-blind; ST, standard therapy; TMZ, trimetazidine.

Trimetazidine has been studied in patients with coronary artery disease and angina with and without co-morbidities. The product has been tested against placebo and the first line anti-anginal drugs; it has also been tested in combination with beta-blockers against placebo, nitrates and calcium channel blockers against placebo and nitrates.

All the above studies have been submitted by the MAHs of trimetazidine containing productsand have been assessed. However, only the studies which were considered most important to support the efficacy on the angina pectoris indication are discussed in details thereafter.

Trimetazidine as monotherapy. Four studies compared TMZ in monotherapy versus placebo, during its early development. These four clinical trials showed that trimetazidine induced improvement on ergometric and clinical parameters when compared versus placebo. Three clinical trials assessed the superiority of TMZ in head-to-head comparisons versus beta-blockers or calcium channel blockers. These studies failed to show the superiority of TMZ vs the active comparators.

TMZ in combination therapy. The evidence supporting the efficacy of TMZ in combination therapy derives mainly from three RCTs evaluating the efficacy and safety of TMZ in combination with beta-blockers (metoprolol or atenolol), and by two studies by Manchanda (1997 and 2003) and four other minor studies assessing TMZ efficacy in combination with calcium channel blockers.

TRIMPOL II (2001)

The aim of this randomised, double-blind, placebo-controlled, study in two parallel groups was to assess the efficacy of treatment of trimetazidine 60 mg/day in patients with persistent stable angina despite treatment with metoprolol 100 mg/day (50 mg b.i.d).

The study included four hundred and twenty-six patients with stable angina and a positive exercise test despite treatment with metoprolol (multi-centre, double-blind, placebo controlled study) who were followed for 12 weeks. All patients had ischaemic coronary disease and stable angina that had lasted for more than three months. Before inclusion, patients had to have positive results in two treadmill exercise tests (with less than 20% variation between the two tests), separated by one week of treatment with metoprolol alone. Patients were included in either the group treated with metoprolol (50 mg twice a day) in combination with placebo t.i.d. or in the group receiving metoprolol in combination with trimetazidine 20 mg three times a day, for 12 weeks.

The treadmill exercise tests (Bruce protocol) were repeated 4 and 12 weeks after inclusion. Eighteen patients withdrew from the study.

The assessment criteria were total duration of exercise time, time to 1-mm ST-segment depression (main criterion), time to onset of anginal pain, mean number of angina attacks per week, mean consumption of short-acting nitrates per week and rate-pressure product.

The statistical analysis was carried out on the intention-to-treat patients (ITT) and per-protocol.

At inclusion, no significant differences were noted between the two groups.

After 12 weeks of treatment in the intention-to-treat population, i.e., 426 patients (211 receiving metoprolol + trimetazidine and 215 receiving metoprolol + placebo), all parameters significantly improved with trimetazidine compared to placebo. This improvement occurred without any change in the haemodynamic parameters and with very good acceptability.

According to the EMA Point to Consider on adjustment of baseline covariates (CPMP/EWP/2863/99), dated 2003, which came into operation after the release of the results of this study, post hoc analyses adjusted for baseline were performed and confirmed the significant superiority of trimetazidine compared to placebo on all ergometric and clinical parameters.

Table 2: Results of the TRIMPOL-II study adjusted on baseline

Trend relative to inclusion (ITT)	MTP +TMZ	MTP +Placebo	Estimated difference TMZ - placebo [95% CI]	p value
1. Variable based on the exercise test				
Total exercise duration (s)	55.6±90.3	33.5±94.4	20.1 [2.8, 37.4]	0.023
Total workload (METs)	1.1±1.7	0.5±1.7	0.54 [0.21, 0.86]	0.001
Time to 1-mm ST segment depression (s)	74.5±107.7	38.3±126.7	33.4 [11.7, 55.0]	0.003
Time to onset of anginal pain (s)	69.5±96.2	34.2±104.6	33.9 [14.0, 53.9]	<0.001
Maximum ST segment depression (mm)	-0.22±0.65	-0.07±0.75	-0.16 [-0.28, -0.03]	0.013
Rate-pressure product (HR x SBP) at peak exercise	653±3397	395±3680	422 [-207, 1051]	NS
2. Angina pain/consumption of short-acting nitrate derivatives				
Mean number of anginal attacks per week	-1.5±2.6	-1.0±4.5	-0.73 [-1.32, -0.2]	0.014
Mean consumption of short-acting nitrates per week	-1.1±2.3	-0.6±3.8	-0.63 [-1.20, -0.05]	0.032

Abbreviations: *MTP, metoprolol; TMZ, trimetazidine. The results are expressed as a mean ± SD. Estimated differences and P value are adjusted on baseline.*

Two patients withdrew due to adverse events, but neither was related to the study medication: one was an exacerbation of coronary heart disease leading to hospitalisation in the metoprolol + placebo group and one was an acute myocardial infarction leading to death in the metoprolol + trimetazidine group.

A sub-group of 94 patients (44 trimetazidine and 50 placebo) who remained symptomatic despite revascularisation within the previous 6 months and treatment with metoprolol as monotherapy was retrospectively analysed (*Ruzyllo, 2004*).

At baseline, the 2 groups were homogeneous with respect to age (55 y) and gender (20% women). Sixty-eight percent had a history of myocardial infarction in the trimetazidine group vs 58% in the placebo group, and 57% had had a previous coronary artery bypass graft vs 39%, respectively, the others having been treated with percutaneous transluminal coronary angioplasty.

Compared to placebo, 12-week treatment with trimetazidine significantly improved time to 1-mm ST-depression by 80 s and exercise duration by 57 s, as well as time to onset angina by 75 s. Weekly numbers of angina attacks and short-acting nitrate use were significantly reduced.

Three mild gastro-intestinal side-effects were reported in the trimetazidine group vs 1 in the placebo group. These data show that the efficacy of TMZ in patients not adequately controlled by metoprolol monotherapy is maintained also in post-revascularised patients with recurrent angina.In conclusion the TRIMPOL II study shows significant additive anti-ischemic and anti-anginal effect of trimetazidine and metoprolol in patients with ischemic heart disease and chronic stable angina not adequately controlled with metoprolole.

The analysis adjusted for baseline levels is in accordance with EMA guidelines and confirms the results of the non-adjusted analysis. The sub-study in patients with recurrent angina supports the anti-anginal effect of trimetazidine added to metoprolol in patients with more severe degree of angina and myocardial ischemia.

Two studies (Sellier et al, 2003; the VASCO study 2011) assessed the efficacy of trimetazidine in combination with atenolol versus placebo.

In both studies atenolol was administered at 50 mg/day of atenolol, a common dosage used in clinical practice and in randomised clinical trials. The difference between the two studies lies in the inclusion criteria. The study from Sellier (2003) included patients with effort-induced myocardial ischemia and

angina while the VASCO study included symptomatic and asymptomatic patients with coronary artery disease.

Sellier study (2003)

The aim of this randomised, double-blind, placebo-controlled, multi-centre study 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 2 months of treatment.

This study was carried out in 223 patients with stable angina out of 818 selected patients (27%). The mean duration of their coronary artery disease (CAD) was 56.3±72.1 months. CAD was class II, according to the classification of the Canadian Cardiovascular Society (CCS), for 68.6% and class III in 31.4% of patients. Patients had experienced during the 3 months preceding the study, an average number of 7.7±7.7 anginal attacks per week. Over half (58.7%) of them had a past history of myocardial infarction. CAD was authenticated by coronary angiography (in 53.2% of male patients and 65% of female patients), a documented history of transmural myocardial infarction (in 46.8% of male patients and 50% of female patients) and a thallium scintigraphy or a stress echo-cardiography, respectively, in 9.8% and 14.8% of male patients. Nearly all (98.7%) of the population had been previously treated for CAD.

Patients had two exercise tests (ETTs) performed 2 weeks' apart (visits W2 and W0) while they were receiving monotherapy with atenolol 50 mg. Patients considered as having 2 positive (ST-segment depression ≥2 mm) and stable ETTs (variation in time to 1-mm ST-segment depression ≤20% between the two ETTs) — according to local readings at the site level—were randomised to receive either trimetazidine MR 35 mg (b.i.d.) or placebo (same regimen) on top of atenolol 50 mg (o.d.). The ST-segment depression of 2 mm was chosen in order to ensure that all the patients were affected by the disease. Actually, this threshold corresponds to the discriminant value, according to ACC/AHA guideline 2002, and thus the test had high specificity (*Gibbons, 2002*).

A third ETT was performed after 8 weeks of treatment (visit W8) for efficacy purposes and was not repeated thereafter. Patients continued the study after W8 in order to assess the safety of trimetazidine over 6 months. All ETTs were performed on ergometric bicycles with electromagnetic brakes, using a standardised exercise protocol starting at 30 watts and which increased by 30 watts every 3 minutes. Patients had to reach the positivity criterion after 6 to 12 minutes of exercise, before reaching predicted maximum heart rate (defined as 220 – age). All ETTs were performed at trough, i.e., 12 hours after last ingestion of the study drug intake and 24 hours after the last ingestion of atenolol.

All ETTs were re-analysed by a core-reading center that validated the inclusion criteria, i.e., the presence of 1-mm ST-segment depression and the stability of the disease. Efficacy was assessed on analyses of covariance carried out in the full analysis set (FAS) and in the per protocol set (PPS). The FAS comprising 173 patients (88 patients in the trimetazidine group and 85 in the placebo group) excluded 19 patients not evaluated after randomisation (11 *vs* 8, respectively) and 24 patients who did not fulfill the criteria of stable angina, as required by the guidelines: 3 patients with no coronary artery disease (2 *vs* 1, respectively) and 21 patients who did not satisfy the stability criterion at baseline (11 *vs* 10, respectively).

The main efficacy criterion was the time to 1-mm ST-segment depression, which is the usual threshold for analysing the anti-ischemic effect of an anti-anginal. For this criterion, the difference between the 2 groups was equal to 34 s, in favour of trimetazidine (p=0.03).

A significant difference was also evidenced for the time to onset of angina pectoris (p=0.049)

Table 3: Primary criterion in the FAS

	Trimetazidine (TMZ) n=88	Placebo n=85	Estimated difference TMZ-placebo[95% CI]	p value
Change in time to 1-mm ST-depression (s)	44.3±113.5	11.6±91.6	34.4 [3.5, 65.2]	0.03

Analysis adjusted for baseline

As the patients had to reach an unusual 2-mm ST-segment depression with the local reading to allow his/her selection and inclusion and as this criterion was not mandatory for the final ETT, the recommended primary criterion "total exercise duration" of the guidelines did not appear as relevant under such conditions.

Indeed, the absence of a recommendation to perform a final test with the same requirements of reaching a 2-mm ST-segment depression could have led the investigators to stop the final test when reaching the usual positively criterion, i.e., 1-mm ST depression with angina pain or 1.5-mm ST depression with no angina pain (Gibbons, 2002). There were no statistically significant differences between the 2 groups for the rate-pressure product at rest and at peak exercise. In addition, there was an improvement in the number of angina attacks per week, which decreased by 34% in the trimetazidine group *vs* 19% in the placebo group.

With regard to safety over the 6-month follow-up, no specific adverse event, ECG abnormality or biological parameter concerns were observed.

VASCO study (2011)

This international multi-centre study (Danchin, 2011) was carried out in compliance with the European guideline for the clinical evaluation of anti-anginal treatments dated 1996, reviewed in 2006.

It evaluated 2 doses of modified release trimetazidine (35 mg bid and 2x35 mg bid) versus placebo, in addition to background beta-blocker therapy at the usual dosage in practice in most countries (50 mg o.d.). Patients were selected and monitored with exercise tolerance tests (ETT) in the selection and inclusion phases, and then at the end of treatment at 12 weeks. To obtain the 1962 (41%) patients who met the inclusion criteria, 4755 patients had to be selected; the others were mostly characterised by non-stability of ETT criteria. The study organisation (supervision committees including one to ensure centralised validation of the exercise tolerance tests) and the study performance conditions (no patient lost to follow-up, acceptable deviation incidence, suitably represented coronary secondary prevention medicinal products) allow the conclusion that the study met the quality criteria required.

The patients included in compliance with the guideline were characterised as follows: coronary artery disease was mostly documented by a history of myocardial infarction or revascularisation or a positive coronary angiography; patients suffering from stable angina for at least 3 months were included based on 2 positive (electrically and clinically) and so-called stable exercise tolerance tests (on both, total exercise duration and time to 1-mm ST-depression criteria), within the individual variation limit of 20% retained by the guideline; and clinical symptomatology and nitrate intake were declared at selection and verified using a diary, over a period of 30 days on average, before inclusion. It should be noted that no minimum incidence of weekly angina attacks was required for inclusion in this population of coronary heart disease patients who were symptomatic on effort.

Actually, in spite of the compliance of ergometric and clinical inclusion criteria with European recommendations, the population of VASCO turned out to have few symptoms, since 20% of the patients reported no angina attacks in the run-in period. Thus 2 populations were included: those who

were symptomatic (n=1574) and who had reported at least 1 angina attack during the run-in phase and those who were not (20% of the patients reported no angina attack nor short-acting nitrate use).

In the overall set, VASCO did not reach its predefined primary objective, to demonstrate a significant difference for at least one of the 2 doses of trimetazidine *versus* placebo on the criterion "total exercise duration," although the higher dosage showed a trend toward statistical significance (p=0.056). However in symptomatic patients (post hoc analyses) receiving trimetazidine 140 mg/day, the increases in total exercise duration (p=0.01), time to 1-mm ST-segment depression (p=0.095) and time to angina onset (p=0.005) were larger than those observed in the placebo group, with relative improvements of 82%, 37% and 43%, respectively.

Table 4: Change in TED, T1 and TOA (in seconds) in ITT population (n=1962, ITT set)

		TMZ 70 mg/day	p^a	TMZ 140 mg/day	p^b	Placebo
	N	654		655		653
TED	Mean ± SD	17.2±65.2	0.370	21.9±72.4	0.056	15.9±67.6
T1	Mean ± SD	25.2±81.3	0.191	26.7±89.7	0.158	22.3±81.8
TOA	Mean ± SD	37.9±79.4	0.201	46.9±91.0	0.004	34.0±80.8

Abbreviations: *TMZ, Trimetazidine; TED, Total exercise duration; T1, Time to 1-mm ST-segment depression; TOA, Time to angina onse.*
p value *adjusted on baseline and countries:* p^a: *p value comparing 70 mg/d vs placebo;* p^b: *p value comparing 140 mg/d vs placebo.*

In addition, a specific focus on the presence of a personal history of heart failure (n=147 patients equally distributed among the 3 groups) showed the benefit of the higher dose of trimetazidine (47 patients) over placebo (51 patients) on the ergometric criteria. The increases in total exercise duration, time to 1-mm ST-depression and time to onset of angina were respectively 34.8 ± 83.1 s (p=0.07), 41.4 ± 97.2 s (p=0.06) and 52.5 ± 82.4 s (p=0.048) with trimetazidine compared to 11.3 ± 67.6 s, 11.2 ± 82.1 s, 24.3 ± 79.3 s with placebo. These figures correspond to an effect about twice that observed with placebo (i.e., 2.2, 2.9 and 1.6, respectively).

The efficacy of TMZ in addition to calcium channel blockers has been evaluated in the two studies by Manchanda (1997 and 2003) and in four other minor studies (Brochier *et al,* 1986; Levy *et al.,* 1995, Bermudez *et al.,* 1995, and Aksoyek *et al.,* 1996). Results from these studies are considered supportive of the efficacy of TMZ in add-on to calcium channel blockers.

The two Machanda randomised clinical trials evaluated the efficacy of the combination of TMZ 60 mg/day in patients suffering from angina pectoris insufficiently controlled on a full dose of diltiazem of 180 mg/day (Manchanda *et al,* 1997) and the efficacy and acceptability of TMZ (60 mg/day) in combination with a low dose of diltiazem (90 mg/day) (Manchanda *et al.,* 2003). The low dose of diltiazem is frequently given in the clinical practice due to poor tolerance of higher dosages, in the symptomatic control of angina. Both studies showed a statistical significant improvement in favour of trimetazidine for the primary endpoint time to 1-mm ST-segment depression and the clinical outcomes and indicate that the addition of TMZ to diltiazem is efficacious whatever the dose of diltiazem received by the patient, 180 or 90 mg/day.

The results from the four minor clinical trials are in line with those of the two Manchanda trials supporting the efficacy of TMZ as add on to calcium channel blockers in patients with angina pectoris.

The efficacy of trimetazidine in the treatment of angina pectoris has been summarised in a recent network meta-analysis including 358 clinical trials and 27,058 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 ETT ergometric parameters. Similar efficacy was observed for clinical symptoms. Trimetazidine improved

the three ergometric criteria by on average a 40-sec increase for TED, 48-sec increase for T1 and 45-sec increase for TOA when compared to placebo. Similarly, the class of other non-HR-lowering anti-anginal agents increased ETT parameters on average by 37 sec for TED, 51 sec for T1 and 46 sec for TOA. The results of this meta-analysis are in line and confirm those of the Cochrane meta-analysis (2005).

The clinical benefit of trimetazidine has also been assessed in at-risk populations: the elderly, diabetics, patients with peripheral artery disease, and patients with left ventricular dysfunction or heart failure. Since 1990 many trials have studied trimetazidine in ischaemic heart failure patients and a recent up-to-date meta-analysis performed by Gao and colleagues (2011), has summarised the positive effect on left ventricular ejection fraction (+7.5%) and even suggested a possible effect on all-cause mortality in a subgroup of 4 studies with this information out of 17 studies in ischaemic heart disease (risk ratio 0.29 [0.17, 0.49]). In summary, the efficacy of trimetazidine in stable angina, as recommended by guideline EMEA/CPMP/EWP/234/95 on clinical investigation of anti-anginal medicinal products in stable angina pectoris, has been demonstrated in mainly in combined therapy versus placebo, and the recent meta-analysis confirms this efficacy.

In conclusion, the CHMP considered that the indication in the '*prophylactic treatment of attacks of angina pectoris'* was not supported anymore by sufficient convincing data. However the CHMP considered that based on the recent clinical studies, a rewording of the indication, 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, is acceptable.

2.2.2 Otology - Ear, Nose and Throat (ENT)

The indication in otology is authorized in 12 European Union Member States. The recommended dosage of TMZ 20 mg is one tablet three times a day, i.e. a daily dose of 60 mg. The equivalent dosage of TMZ 35 mg is one tablet in the morning and one tablet in the evening at mealtimes, i.e. a daily dose of 70 mg.

The mechanism of action whereby trimetazidine is suggested to improve the symptoms of vertigo and tinnitus can only be described within the limits of knowledge of the pathophysiology of these symptoms. Animal models have provided some information on the action of trimetazidine in impaired cochleo-vestibular function.

Table 5 Clinical studies on the efficacy of vertigo and tinnitus

Study	Date carried out No. of centres/countries	Design	Duration	n	Inclusion criteria	Symptoms at inclusion		
						Vertigo	Tinnitus	Hypoacusis
Inclusion for "vertigo and/or tinnitus" or "vertigo"								
Studies *versus* placebo								
(Wayoff, 1984)	1983 / 15 / France	R, DB, 2 PG, Pla	2 months	334	**Cochleovestibular disorders**	64 %	79 %	81%
(Sterkers, 2001)	1997-1998 / 6 / France	R, DB, 2 PG, Pla	2 months	28	**Vertigo**	**100%**	50%	39%
(Vitte, 2002)	1999-2000 / 2 / France	R, DB, 2 PG, Pla	2 months	53	**Vertigo**	**100%**	60%	53%
Studies *versus* betahistine								
(Haguenauer, 1980)	1976 / 1 / France	R, DB, 2 PG, Beta	3 months	40	**Vertigo**	**100%** (including 50% Meniere)	85%	93%
(Kluyskens, 1990)	1988 / 1 / Belgium	R, DB, 2 PG, Beta	3 months	40	**Vertigo**	**100%** (including 50% Meniere)	58%	70%
(Martini, 1990)	Italy	R, DB, 2PG, Beta	2 months	45	**Meniere's disease**	100% Meniere's disease (vertigo, tinnitus, hypoaccusis)		
Inclusion for "tinnitus"								
Studies *versus* placebo								
(Morgon, 1990)	1987-1988 / 13 / France	R, DB, 2 PG, Pla	2 months	315	**Tinnitus**	23%	**100 %**	70%

R : Randomised, DB : double-blind, PG : Parrallel groups, Pla : Placebo, Beta : Betahistine

The efficacy of trimetazidine in the treatment of peripheral vertigo with or without cochlear symptoms has been studied in three randomised, double-blind trials versus placebo: The Wayoff study, (1984) investigated the efficacy of 20-mg trimetazidine twice daily while more recent studies (Pilot Sterkers study, 2001;Vitte study, 2002; and a pooled analysis on the patient's Quality of Life self-assessment clinical questionnaire /DHI) studied the effect of trimetazidine at a dose of 35 mg twice daily. Three studies have also been conducted versus betahistine (Haguenauer, 1980 and Kluyskens, 1990 and Martini, 1990).

In the treatment of tinnitus, the efficacy of trimetazidine has been documented in two randomised double-blind, placebo-controlled studies (Wayoff, 1984 and Morgon, 1990) using 20-mg trimetazidine twice daily in comparison with placebo.

The “France-Cochlée” Study (Bouccara, 2009) evaluated the course of presbyacusis in a population over the age of 40 years and the therapeutic effect of trimetazidine on deterioration of presbyacusis while the Haguenauer study (1990) assessed the efficacy of trimetazidine in patients suffering from degenerative deafness.

Efficacy in Vertigo

Three studies versus placebo which were conducted after the initial Marketing Authorisation, have been submitted: Wayoff *et al.,* 1984, Sterkers *et al.,* 2001 and Vitte *et al.,* 2002.

Wayoff study (1984). This was a placebo-controlled, randomised, multicentre, double-blind, parallel groups study, in patients with one or more symptoms of a cochleovestibular disorder (vertigo and/or tinnitus and/or hypoacusis). Fifteen centers included 334 patients (TMZ 166 / Placebo 168) in total, of whom 272 (81%) completed the study (TMZ 135 / Placebo 137). The statistical analysis was performed on those 272/334 patients who underwent three successive examinations.

Vertigo was assessed in subgroups of patients. The evolution of the clinical symptomatology was reported by 179 patients (87 in the trimetazidine group, 92 in the placebo group) presenting dizziness among the 272 patients of the overall analysed population. Results showed statistically significant difference for improvement of the vertiginous symptomatology over time in favour of trimetazidine for all scores collected (intensity, duration, frequency; $p < 0.0001$ vs placebo).

The study used diagnosis and evaluation methods available in the early 80s. The study presented several methodological deficiencies.

The recruitment of patients was undertaken on a wide inclusion criterion (functional cochleovestibular symptomatology including several symptoms) but the etiological diagnoses have not been described. The study aimed at evaluating several symptoms: dizziness and/or tinnitus and/or hypoacusis. Many endpoints were assessed, without any of them being predefined as primary, and this was done without any discussion of the impact on the type I error.

It is considered that due to the above mentioned deficiencies, the Wayoff study is not adequate to demonstrate the clinical benefit of trimetazidine in the treatment of vertigo symptoms.

Sterkers study (2001). This double-blind, randomised pilot study comparing trimetazidine 35 mg *versus* placebo was aimed at determining the number of patients required, to demonstrate a difference between trimetazidine and placebo at an α risk of 5% and a minimum power of 85%, the final objective being the drafting of an efficacy study protocol in the "vertigo" indication.

Of the 28 randomised patients (15 in the trimetazidine group, 13 in the placebo group), 24 completed the study. 4 withdrew from the study: 2 in the trimetazidine group (1 for adverse event, 1 for inefficacy), 2 in the placebo group (1 for adverse event, 1 for non-medical reason). In terms of results, the scale evaluating the impact on daily life and the visual analogue scale were shown not to be sensitive and were therefore not retained for further investigations. The psychiatric scale was considered of little interest as there was a low initial degree of anxiety and no variation was observed, irrespective of the treatment group.

The Dizziness Handicap Inventory (DHI) questionnaire was retained as promising. This is a specific validated multidimensional questionnaire measuring the deterioration of the patient's health-related

quality of life due to vertigo (Jacobson, 1990). The DHI contains 25 items, and a total score (0-100 points) is obtained by summing ordinal scale responses, higher scores indicating more severe handicap. The scale was developed to capture various sub-domains of self-perceived handicap and comprises 7 physical, 9 functional, and 9 emotional questions. Interestingly, Jacobson showed that the 'emotional' handicap subscore score was correlated to the frequency of vertigo attacks.

The responses on the DHI were very different depending on the sub-scores. A better response of TMZ over placebo was observed on the "emotional" sub-score compared to the "physical impact or functional" sub-scores. However, these results were obtained on 11 subjects versus 10 subjects. A great variability due to the low number of patients was observed. The study did not comprise any inter-group comparisons (TMZ vs placebo), and thus it is not considered supportive of any clinical benefit. Furthermore, the electronystagmographic results (effect on hypovalency and on directional preponderance) were not consistent. The overall impression of the investigator showed that 6 patients improved and greatly improved in each group (TMZ 6/12 vs placebo 6/11). Some results were not found in the report (e.g. according to the protocol, results from a patient record aimed at reporting intensity, frequency and duration of vertiginous episodes should have been provided but these results cannot be found).

In conclusion, the exploratory nature of the study, the absence of inter-group comparisons and the extremely small population do not allow any conclusion on the efficacy of TMZ in treating vertigo on the basis of this study.

Vitte study (EquiTest & DHI) (2002). This multicentre, double-blind controlled study compared the effect of trimetazidine 35 mg × 2/day (70 mg) *versus* placebo after 8 weeks of treatment in peripheral vestibular disorders.

53 patients were recruited in 14 centres. Seven patients (13.2%) discontinued the treatment, of whom 4 (14.8%) in the trimetazidine group (1 due to lack of efficacy, 1 due to remission and 2 for non-medical reasons). Forty eight of the 53 randomised patients (91%) had vestibular hypovalency and 33/53 (62%) had directional preponderance.

As regards the Dizziness Handicap Inventory (DHI), similarly as the Sterkers study, the emotional impact subscore is the only one that showed the significant favourable progress, with a reduction of -7.6 ± 8.6 in the trimetazidine group, versus -3.0 ± 4.1 in the placebo group; estimated treatment effect -3.4 ± 1.6 (p = 0.037). No statistically significant differences between groups were observed for the overall score or other DHI sub-scores (p=0.134; p=0.202; p=0.361).

Pooled analysis for the Dizziness Handicap Inventory (DHI) in vertigo (Sterkers+ Vitte).

A pooled analysis of DHI score of the pilot study (Sterkers) and the Vitte study was also provided. This is a new analysis which was not submitted during the assessment or re-assessment carried on by the French national authority. Considering that the two studies were very similar (equivalent inclusion criteria, the same experimental design) the pooling of data can be accepted.

Data from patients in Sterkers' pilot study (2001) and Vitte's study (2003) were pooled (N=66) in an intention-to-treat (ITT) analysis of responses to the DHI (see table below).

Table 6 Treatment effect on the DHI scores of pooled data (FAS).

	DHI scores Mean (SD)	Trimetazidine N=33	Placebo N=33
Global score (/ 100)	M0 Baseline	38.4 (17.1)	36.9 (17.2)
	M2 End point	20.6 (18.8)	25.9 (21.1)
	Absolute Change	-17.8 (20.5)	-10.9 (17.2)
	Difference*	-6.2 (4.3)	
	95% CI	[-14.8; 2.5]	
	p**	0.157	
Functional Score(/ 36)	M0 Baseline	14.5 (7.1)	13.9 (7.6)
	M2 End point	8.1 (7.8)	9.3 (8.5)
	Absolute Change	-6.4 (8.9)	-4.7 (7.2)
	Difference*	-1.5 (1.8)	
	95% CI	[-5.1; 2.1]	
	p**	0.412	
Emotional Score (/ 36)	M0 Baseline	12.9 (7.8)	10.7 (6.9)
	M2 End point	6.0 (7.0)	7.9 (7.8)
	Absolute Change	-6.9 (9.0)	-2.8 (4.1)
	Difference*	-3.1 (1.6)	
	95% CI	[-6.2; 0.0]	
	p**	0.050	
Physical Score (/28)	M0 Baseline	11.0 (5.8)	12.2 (6.0)
	M2 End point	6.6 (5.9)	8.8 (7.3)
	Absolute Change	-4.5 (6.0)	-3.5 (8.6)
	Difference*	-1.8 (1.6)	
	95% CI	[-5.0; 1.3]	
	p**	0.253	

** adjusted on baseline value; SD : standard deviation; CI : confidence interval*
***p-value of the co-variance analysis*

After two months of treatment, no statistically significant differences between groups were observed for the total population, on the overall score and the three DHI sub-scores.

As no lower limit had been set for the DHI score to enter these studies, some of the patients did not display any significant degree of vertigo-related handicap at baseline. Based on the demonstrated correlation between the frequency of occurrence of vertigo episodes and the DHI scores (global, functional and emotional ones, the treatment effect on the DHI score was also performed in a subgroup analysis in patients with a minimal perceived handicap (N=37). With respect to the 2-month treatment period, the DHI global score of 34.2 at baseline, corresponding to >12 attacks per year, or >1 attack per month (Jacobson, 1990), was selected as being a relevant cut-off.

	DHI scores Mean (SD)	Trimetazidine N=19	Placebo N=18
Global score (/ 100)	M0 Baseline	56.2 (3.7)	53.9 (2.9)
	M2 End point	25.8 (4.9)	39.2 (4.9)
	Absolute Change	-30.4 (5.0)	-14.7 (4.6)
	Difference*	-14.7 (6.6)	
	95% CI	[-28.0; -1.3]	
	p**	**0.032**	
Emotional Score (/ 36)	M0 Baseline	19.6 (1.7)	15.2 (1.8)
	M2 End point	7.6 (1.8)	12.4 (2.2)
	Absolute Change	-12.0 (2.2)	-2.8 (0.9)
	Difference*	-7.8 (2.4)	
	95% CI	[-12.7; -2.9]	
	p**	**0.003**	

In this small subgroup of selected patients, it was shown that after 2 months of treatment, the differences between TMZ and placebo were statistically significant for the global score (p = 0.032) which improved by 54.3% with TMZ versus 26.3% with placebo. Among the sub-scores, the emotional score significantly improved by 58.0% versus 26.0% with the placebo (p = 0.003), followed by the functional, which improved by 52.3% vs 23.7% respectively score (p=0.079), and to a lesser extent the physical score improved by 45.6% vs 20.7%.

It is considered that this additional analysis on a subgroup determined a posteriori can only be viewed as exploratory and therefore, is not adequate to show improvement of quality of life with TMZ In patients with vertigo.

Three studies (Haguenauer, 1980; Kluyskens, 1990; Martini, 1990) evaluated the efficacy of trimetazidine in the treatment of dizziness in comparison with betahistine. None of these three studies was predefined as non-inferiority study; therefore, the results which were presented as supportive of similar efficacy are deemed not reliable.

Efficacy in tinnitus

In the treatment of tinnitus, the efficacy of TMZ has been documented in two randomised double-blind, placebo-controlled studies (Wayoff, 1984 and Morgon, 1990) using 20-mg TMZ twice daily in comparison with placebo. However, only the results from Morgon study have been discussed at length due to the fact that this study recruited only patients presenting primarily with subjective tinnitus with or without associated hypoacusis, tinnitus being the reason for consulting the doctor in the first place, whereas the Wayoff study recruited a broader patient population presenting one or more symptoms of a cochleovestibular disorder with vertigo and/or tinnitus and/or hypoacusis. The Morgon study (1990) was a double blind placebo-controlled, two-month clinical study carried out in 315 patients. Patients in this study were assessed both subjectively (using numerical symptom scores) and objectively by means of tinnitus matching audiometry (Fowler's comparative test and tinnitus masking test).

After 8 weeks of treatment, the intensity and frequency of the tinnitus regressed by 26% and 23% with trimetazidine versus 14% and 12% with placebo, these differences were statistically significant (p = 0.025 and 0.001, respectively), but of limited clinical relevance.

In tinnitometry the two methods of objectively measuring tinnitus intensity, the Fowler's technique (or the comparative balance method) and the technique of masking the affected ear, reported significantly greater decrease in the mean intensity in decibels in the trimetazidine group than in the placebo group (p = 0.007 and p = 0.026, respectively).

Despite some encouraging results, no conclusion can be drawn from this study due to a number of major methodological weaknesses: i) The protection of the blind cannot be evaluated in the absence of elements on the maintenance of the seals of the envelopes containing the randomisation codes, and on their true opacity. ii) There was a significant number of dropouts; no analysis was conducted in Intention-to-Treat (ITT) including all patients randomised, and using a suitable procedure for processing missing data; iii) The great number of evaluation criteria were not hierarchized and the impact of the multiplicity of statistical comparisons on the type I error were not taken into account. iv) Furthermore, considering the nature of the criteria, comparisons in terms of responders would have been more appropriate to assess the clinical relevance of the results (for example: patients improving by at least one grade). It is noted in fact that the differences observed at two months seem very low to constitute a real clinical benefit for the patients.

In conclusion, the evidence in favour of the efficacy of trimetazidine in tinnitus is not supported by the clinical data.

Efficacy in hypoacusis

The “France-Cochlée” Study (Bouccara, 2009,) evaluated the course of presbyacusis in a patient population aged 40 years or more, and the therapeutic effect of TMZ on deterioration of presbyacusis; the Haguenauer study (1990) assessed the efficacy of TMZ in patients suffering from degenerative deafness.

The Bouccara study (2009) is the largest and longest term intervention trial performed to date in middle-aged patients with progressive hearing loss for high pitch sounds, characteristic of presbyacusis. It was carried out versus placebo. The mean treatment duration was less than three years.

Even though the “presbyacusis” indication is not in the current scope of the indications of the marketing authorisation of trimetazidine, it is noted that this recent study did not show any significant clinical benefit in favour of patients treated with trimetazidine compared to placebo.

The Haguenauer study (1990) was a multicentre randomised, parallel-group study to compare the effects of 60 mg/day of trimetazidine to those of a placebo, in patients with degenerative deafness, during 6 months. No complete report of this study has been provided and information from the published data of Haguenauer 1990 is scarce. After 6 months of treatment significant differences in pure tone audiometry curve, speech audiometry and subjective evaluation of hearing loss were reported in favour of TMZ ($p=0.002$; $P = 0.008$ and $P < 0.001$). However, no primary outcome was initially defined and the multiplicity of the criteria analysed was not taken into account. Therefore, the results cannot be accepted as proof of efficacy.

Thus no positive conclusion can be drawn on the efficacy of TMZ in patients with degenerative deafness.

2.2.3 Ophthalmology

Trimetazidine is indicated in Ophthalmology in 7 countries in the European Union.

An example of the registered indication in ophthalmology (France), “*Adjuvant treatment of the decline in visual acuity and visual field disturbances presumably of vascular origin*”, shows that this is a general indication covering a very wide range of ocular diseases.

In all countries, the recommended dosage of trimetazidine 20 mg is one tablet three times daily, i.e. a daily dose of 60 mg and the equivalent dosage of trimetazidine 35 mg is one tablet morning and evening, i.e. a daily dose of 70 mg.

Nine clinical studies which were conducted after the initial marketing authorisation, are available: Three pharmacodynamic double-blind versus active comparator studies, the Cordella study (1983), the Cornand study (1982), the Perdriel study (1988). Three randomised double-blind placebo controlled clinical studies: Couderc and Lebuisson study (1984), Aron- Rosa study (1988), Cohen (2011). In addition, an exploratory study (Nowak 2007) and two cohort open studies (Guillaumat, 1982 and Millara 1988) were also performed. Data from comparative studies used reference products no longer recognised as relevant treatments for retina diseases or glaucoma, i.e. cinnarizine, piridoxilate or ginkgo biloba.

Among the nine clinical studies submitted in support of the ophthalmologic indication of trimetazidine in this re-evaluation dossier, eight were conducted with the 20 mg dosage.

Study versus cinnarizine (Cordella, 1982; Cordella, 1983)

This was a double-blind, randomised, controlled study, comparing trimetazidine tablet or oral drops 20 mg (60 mg/day, i.e. 20 mg tid) versus cinnarazine (75 mg/day, i.e. 20 drops tid) over 2 months, in patients presenting evidence of exudates, atrophy or vascular disorders of retina, either as a primary manifestation or in the form of recurrence.

Twenty four patients were involved in this trial (29 eyes). Patients included presented very heterogeneous pathologies (e.g. macular exsudate, pigmented epithelium detachment, macular pseudo-hole, central serous choroiditis, macular edema, macular atrophy, diabetic retinopathy, partial occlusion of central vein of retina, degenerative myopia, etc.) with absence of prior stratification on these pathologies.

The macular functional disorders evaluated using the Amsler test were reported as disappearing in 7 eyes out of 8 in the patients taking TMZ tablets and in 6 out of 6 eyes in the group taking TMZ drops while it disappeared only in 2 eyes out of 6 in the cinnarazine group.

Although no significant differences between the three groups were evidenced these results were no statistically significant.

Perdriel study, versus piridoxilate (Perdriel, 1988).

This was a randomised, single blind, crossover study comparing the effect of single intravenous injections of TMZ (20 mg) and piridoxilate (400 mg), in 8 patients suffering from retinal arteriosclerosis. The two phases of the cross-over study were separated by 8-day period.

In both phases, the endpoints were the variations in maximum amplitude of the negative “a” and positive “b” waves in the electroretinogram (ERG).

Intra-group comparison results on waves’ amplitude were as follows:

1. The mean maximum amplitude of the "a wave” significantly increased compared to baseline after single IV injection of 20 mg of TMZ ($p< 0.001$) or of 400 mg of reference product ($p< 0.01$) at all time points (10, 20, 30 and 40 mn).
2. Compared to baseline, the maximum amplitude of the "b wave” significantly increased after the same administration of 20 mg of TMZ ($p< 0.001$) at all time points, while it was not modified by Piridoxilate, the reference product (NS).
3. Trimetazidine : In percentage terms, after 20 min the amplitude of the “a wave” increased by 15.4% and that of “b wave” had increased by 8%; after 40 mn, values of “a wave” and “b wave” began to decline (respectively, +14.5% and +7%).
4. Piridoxilate: In percentage terms, after 30 minutes the amplitude of the “a wave” increased by 11.1% and after 40 minutes, that of “b wave” decreased by 1.5%.

Inter-group comparison results were as follows:

1. No statistically significant difference (NS) between TMZ and reference product was evidenced for amplitude of the "a" wave.
2. With the limitations of this exploratory study, the activity of TMZ, on the b wave, administered as single IV injection, was reported to be significantly superior to that of piridoxilate at each test time ($p<0.001$).

Study versus placebo, Couderc and Lebuisson study (Couderc, 1984)

This study was double blind, conducted versus placebo and in parallel groups in adult patients from different chorio-retinal diseases who received trimetazidine 20 mg tablets 3 times a day (60 mg/day).

The *therapeutic activity* was evaluated before and after treatment via the measurement of number of criteria: distant and near visual acuity using respectively, Monoyer scale and Parinaud scale, visual field using a Goldman perimeter, examination of the fundus oculi and fluorescein angiography. The last three parameters were evaluated according to three possible outcomes: improvement, no change or progression of the disease.

A total of 32 patients were treated (17 patients received TMZ 60 mg daily and the other 15 patients a placebo).Patients received either trimetazidine for 124.19 days on average, or a placebo for 106.36 days on average.

The analysis is reported to be done on 31 patients. The overall evolution of the subjects presenting with highly heterogeneous pathologies did not show any significant difference between the two groups.

Study vs placebo, France DMLA 2 Study (Cohen, 2011.)

This multicentre, randomised, controlled, double-blind study on two parallel groups compared 70 mg of TMZ (2 tablets daily of modified release TMZ at 35 mg) to placebo, administered for 3 to 5 years with stratifications on the age, gender and type of ARMD lesions on the studied eye, in order to evaluate the therapeutic efficacy of TMZ in the slowing of Aged-related macular degeneration (ARMD) progression.

1,192 patients presenting ARMD were included and randomised. A total of 358 (33%) patients developed neovascularisation during the study (TMZ: 181 / 33% – Placebo (P): 177/ 33%). The incidence of neovascularisation per 100 patients-years was of 10.86 (TMZ) and 11.13 (P). The difference between groups was not significant (hazard ratio between groups (HR) of 0.97 (95% CI: [0.77; 1.20]). The difference between groups was not significant (p=0.781).

TMZ failed to prevent choroidal neovascularisation. Although subgroup analyses suggested that TMZ could be tested as preventive therapy for geographic atrophy, the overall comparison showed no statistically significant differences in the progression of geographic atrophy.

Uncontrolled studies and cohort studies

Three uncontrolled studies: an exploratory study (Nowak 2007) and two cohort open studies (Guillaumat, 1982 and Millara 1988) were submitted, the results of which are not discussed as they do not add information in favour of a beneficial effect of TMZ in the ophthalmology indications.

2.2.4. Discussion on efficacy

Angina pectoris

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

Four studies compared trimetazidine in monotherapy versus placebo, during its early development as requested by the development guidelines in force at the time of the studies. These four old clinical trials showed that trimetazidine induced improvement on ergometric and clinical parameters when compared versus placebo. According to the EMA guideline on angina, superiority compared to placebo should be shown before conducting add-on studies. The CHMP noted that, due to the design and the regimen used, these studies can be considered as supportive for the add-on indication, but are not adequate to support the monotherapy indication. Similar conclusions are drawn for the three clinical

trials performed to assess the superiority of trimetazidine in head-to-head comparisons versus beta-blockers or calcium channel blockers. The CHMP acknowledged that these studies did not show any significant difference between trimetazidine and active comparators, but stated that it is not possible to conclude, on the basis of these results, that there is no difference between the study drugs.

The CHMP concluded that the limited evidence available for the efficacy of trimetazidine in monotherapy, although considered supportive for the add-on indication, is considered no more adequate to support its use in monotherapy in alternative to first line anti-angina drugs.

The CHMP considered that the evidence generated by the most recent studies questions the efficacy of trimetazidine in the treatment of angina pectoris. It is considered that the main set of data in support of the add-on indication of trimetazidine in symptomatic patients with angina are derived from the TRIMPOL-II study (2001), the study by Sellier (2003) and the revised data from the VASCO study (2011). 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

In the randomised, double blind, placebo-controlled study (TRIMPOL-II) performed in 426 patients, trimetazidine (60mg/day) added to metoprolol 100 mg daily (50 mg b.i.d) for 12 weeks significantly improved statistically exercise tests parameters and clinical symptoms as compared to the control arm: 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. No undesirable hemodynamic changes were observed with trimetazidine.

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 today accepted standards, no major bias affecting the interpretation of study results appears evident and all analyses consistently show a beneficial effect of trimetazidine combined with metoprolol on exercise tolerance, myocardial ischemia and clinical symptoms. The post-hoc analysis in 298 patients of this study receiving trimetazidine on top of the maximum tolerated dose of metoprolol further confirms the benefit of trimetazidine 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 of trimetazidine was confirmed in patients at maximal dose of metoprolol as well as in patients with recurrent angina.

The aim of the double blind, placebo-controlled study by Sellier (2003), was to assess the efficacy of trimetazidine modified release (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 The study randomized 223 patients who received one 35 mg trimetazidine modified release tablet (b.i.d.) added to 50 mg atenolol (o.d.) for 8 weeks or 50 mg atenolol (o.d). Results showed a significant difference in favour of trimetazidine (+34.4s adjusted for baseline, p=0.03) on the primary outcome 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). This was expected as the Sellier study was an exercise study not primarily designed to assess clinical parameters. In double-blinded VASCO study (2011), 1,962 patients were randomized to receive either, two dosages of trimetazidine (70 mg/d and 140 mg/d) on top of atenolol 50 mg/d, or atenolol combined with 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 a post-hoc analysis in the subgroup of symptomatic patients (n= 1,574) the patient population for which the CHMP considered that a positive benefit/risk of trimetazidine is currently demonstrated, 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.

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-angina treatments are ineffective in improving exercise capacity. Thus, the results obtained with trimetazidine in the subgroup population of symptomatic angina patients support trimetazidine efficacy.

The efficacy of trimetazidine was also summarised in a recent network meta-analysis including 358 clinical trials and 27,058 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 ETT ergometric parameters. The results of this meta-analysis are in line and confirm those of the previous 2005 Cochrane meta-analysis.

On the basis of this evidence, the CHMP concluded that the efficacy of trimetazidine is sufficiently demonstrated as add-on therapy in the treatment of symptomatic patients with angina who are inadequately controlled by or intolerant to first-line antianginal therapies. The revised indication is in line with the scientific evidence available at present for trimetazidine as add-on therapy and is supported by trials considered to be of sufficient methodological quality and by meta-analyses that have come to similar conclusions.

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, ten clinical studies were submitted or presented as literature references. Most of these studies included patients presenting very heterogeneous pathologies of various severities and no prior stratification on the basis of these pathologies. The studies were very limited duration (between 2 and 3 months) not in line with what is required by these pathologies that necessitate long term treatments.

These studies aimed at demonstrating the clinical benefit of TMZ in the treatment of tinnitus and/or dizziness and/or hearing loss, thus targeting pathologies that overall correspond to the wording of the registered indications in Europe.

Most ENT clinical trials have been conducted with the 20 mg dosage of TMZ. In some studies the daily dose was lower (40 mg/day) than those recommended in the marketing authorisation (60 mg/day or 70 mg/day), this affects the strength of the efficacy results and limits of the interpretation of the safety data.

Five studies were conducted against placebo. These studies generally included multiple objectives (pharmacodynamic or clinical endpoints) and ENT pathologies and symptomatologies from different etiologies such as tinnitus, different kinds of vertigo or deafness. The Wayoff study (tinnitus, dizziness, hearing loss) and the Morgon study (tinnitus) are the main studies conducted against placebo. These studies (conducted in 1984/1990) and their results, often presented as statistically in favor of TMZ, are disputable mainly for methodological reasons. Two additional and more recent studies were focused on dizziness, the Sterkers study (2001) and the Vitte study (2002). However, the exploratory nature and the extremely small population included (28 patients) in the Sterkers study, together with the

methodological weakness of the Vitte study do not allow any sound conclusion on the efficacy of TMZ in dizziness. Three studies (Haguenauer, 1980; Kluyskens, 1990; Martini, 1990) evaluated the efficacy of TMZ in the treatment of dizziness in comparison with betahistine. None of these three studies was predefined as non-inferiority study; therefore, the results which were presented as supportive of similar efficacy are not reliable.

Additional evidence from the literature consists of pre-clinical data showing possible mechanisms of action through which TMZ could exert beneficial effects on cochleovestibular functions (effects of TMZ in a hypoxia model, anti-free radical effects and effects on the homeostasis of calcium, protective effect against excitotoxic amino acids, effects on the synthesis of complex lipids of the cochlea). These data are considered suggestive of a potential cyto-protective activity of TMZ that could be of some benefit in ENT pathologies. However, this evidence is of limited value in the absence of any clinical demonstration of efficacy.

In conclusion, the evidence of the efficacy in the ENT indication, initially suggested by the studies on the basis of multiple assessments, is considered weak due to the methodology applied to the investigation. The limited data generated by the clinical trials submitted for the ENT indication, insufficiently support the demonstration of a relevant clinical benefit of TMZ for patients suffering from tinnitus, vertigo or hearing loss.

Ophthalmology

Nine clinical studies have been submitted in support of the ophthalmologic indications. Most trials have been conducted with the 20 mg dosage but in some studies daily doses (20mg and 40 mg/day) were lower than those recommended in the current marketing authorisation (60 mg or 70 mg).

Almost all studies suffer from methodological flaws. Three are non-comparative studies conducted in patients with heterogeneous ocular disorders; three are comparative studies of short duration (up to 3 months) conducted against reference products that are no more considered as therapies of choice to treat or prevent retinal or glaucoma diseases; two are studies conducted against placebo including a small number of patients (n=32 and n=242). Most are short-term studies (2 and 6 months) considered not adequate to evaluate the outcome of slow progressing diseases, and include patients presenting very heterogeneous pathologies of various severities.

The additional evidence from the literature consists of pre-clinical data showing possible mechanisms of action through which TMZ could exert beneficial effects on visual functions (effect of TMZ on retinal lesions induced by oxygen free radicals, neuroprotective effect with regard to glutamatergic excitotoxicity, effect on intraocular pressure in rabbits, or protective effect of the retina against ischaemic lesions induced by pressure). These data are considered suggestive of a potential cyto-protective activity of TMZ that could be of some benefit in ophtalmology pathologies. However, this evidence is of limited value in the absence of any sound clinical demonstration of efficacy.

In conclusion, based on the data submitted for the ophthalmologic indication, the CHMP considered that the evidence was limited by the methods of investigation in the ophthalmologic field and it 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 so called reference products or based on cohorts without comparator provide insufficient demonstration of a relevant clinical benefit for TMZ in the ophthalmology indication.

2.3. Clinical safety

Several MAHs have provided responses of the safety questions from CHMP. In this part of the report a summary of the main safety issues is provided. A cumulative review of all spontaneous adverse drug reactions (ADRs) was performed including data from 15 December 1964 (first worldwide Marketing Authorisation of trimetazidine) to 29 May 2011 (Data Lock Point).

In this cumulative review a crude estimate of patient exposure to trimetazidine was calculated on the basis of the sales volumes from prescription. The estimation is based on a mean daily dosage of 2.8 tablets per day and a mean number of 30.4 days by month. The estimated numbers of patients exposed since market introduction is estimated to be 532,544,831 patient-months. During the concerned period, there were 1,019 patient-cases reported (1,916 events), of which 475 serious and 544 not serious.

The most frequently reported ADRs belong to the following System Organ Classes:

- Nervous system disorders (354 events),

- Skin and subcutaneous tissue disorders (211 events),

- General disorders and administration site conditions (208 events),

The most frequently reported reactions were presented in the table below by SOC, corresponding to the number of events:

System Organ Class	**Listed / Unlisted**	**Serious events**	**Non serious events**	**Sub-total**
ALL events		**1055**	**861**	**1916**
Nervous system disorders		**173**	**181**	**354**
Parkinson's syndromes and related disorders,				197
(number of patients)		*(67)*	*(94)*	*(161)*
Including Extrapyramidal disorder	Listed	17	8	25
Parkinsonism	Listed	25	30	55
Tremor	Listed	17	29	46
Headache	Listed	6	25	31
Dizziness	Listed	8	29	37
Skin and subcutaneous tissue disorders		**113**	**94**	**211**
Pruritus	Listed	17	9	26
Rash	Listed	6	16	22
Urticaria	Listed	11	15	26
General disorders and administration site conditions		**86**	**122**	**208**
Asthenia	Listed	5	14	19
Gait disturbance	Listed	5	14	19
Malaise	Listed	17	11	28
Gastrointestinal disorders		**74**	**113**	**187**
Diarrhoea	Listed	12	19	31
Nausea	Listed	6	30	36
Vomiting	Listed	11	13	24
Blood and lymphatic system disorders		**115**	**27**	**142**
Agranulocytosis	Unlisted	16	1	17
Neutropenia	Unlisted	15	0	15
leukopenia	Unlisted	4	1	5
Thrombocytopenia	Unlisted	33	22	55
Thrombocytopenic purpura	Unlisted	13	0	13
Injury, poisoning and procedural complications		**99**	**24**	**123**
Fall	Listed	57	5	62
Vascular disorders		**56**	**27**	**83**
Hypotension	Listed	14	8	22

Orthostatic hypotension	Listed	30	4	34
Psychiatric disorders Insomnia, nightmare, sleep disorders. Confusionnal state, disorientation, hallucinations, aggression.	 Listed Unlisted	**39** 1 28	**39** 14 4	**78** 15 32
Hepatobiliary disorders Hepatitis (cytolytic, acute, cholestatic, fulminant, autoimmune)	 Unlisted	**31** 24	**2** 1	**33** 25
Metabolism and nutrition disorders Hyponatraemia	 Unlisted	**39** 17	**5** 0	**44** 17
Ear and labyrinth disorders Vertigo	 Unlisted	**11** 7	**40** 22	**51** 29
Eye disorders Vision blurred or reduced or impaired	Unlisted	**14** 5	**19** 7	**33** 12

The most frequent ADRs belong to SOC 'Nervous system disorders' with 286 cases including 354 reactions. More than 50 % of the reported ADRs were related to Parkinson's syndromes and related symptoms (161 cases, 197 reactions).

This SOC is followed by the SOC 'Skin and subcutaneous disorders' (211 reactions) and 'general disorders and administration site conditions' (208 reactions).

SOC 'psychiatric disorders' includes 78 ADRs (53 cases) of which 32 were related to agitation, confusion, hallucinations together with 15 reactions of sleep disorders (including 8 insomnia) indicate that trimetazidine may induce psycho-stimulant effects.

A summary of ADRs from 7 clinical studies (including VASCO, Emeriau, France Cochlée, France DMLA-2) showed that sleep disorders –mainly insomnia- are two fold more frequent in the trimetazidine group (38 cases, 1.01 %) than control group (20 cases, 0.56 %). The other medical conditions, observed with trimetazidine were 'fall/hypotension/dizziness' and 'headaches'.

Parkinson syndrome and related symptoms

Parkinson syndrome and related symptoms reported with trimetazidine are rare (161 cases, 0.36/100,000 patient-years (PY)) and in general reversible (79.3%).

A summary analysis of these events form post marketing spontaneous reports is presented hereafter:

- 161 cases were collected 67 of which were serious;
- parkinsonian symptoms were more frequently reported in female patients (62.1%);
- 80.1% of the patients were older than 65 years and 49.7% of the patients were older than 75 years;
- cases were more frequently reported when trimetazidine was prescribed for Ear Nose Throat indication (34.2%) than for angina (21.6%) or ophthalmic indication (9.9%);
- in 20.5% of the cases, patients received trimetazidine in combination with drugs for which this reaction has been described and 30.4% had a relevant past medical history, including Parkinson's disease and parkinsonism (5.6%), dementia (4.3%) and diabetes (9.3%);
- In 37.3% of the cases, the events occurred within one year after trimetazidine initiation, and in 8.7% over 10 years of treatment;

For 135 cases the outcome was known and assessed of which 102 patients recovered, or were recovering, after trimetazidine interruption. At the time of the assessment 78 patients recovered; among them, 57 patients were not concomitantly treated with a drug capable of inducing parkinsonism and had no relevant medical history. Twenty-four patients were recovering after trimetazidine interruption, at the time of reporting. Twenty three patients did not recover after trimetazidine interruption (9 cases were serious). Among them, 7 patients had a relevant medical history (Parkinsonism (1), tremor (1), dementia (2), depression (1), and diabetes (2)) and 5 patients were treated with a drug capable of inducing parkinsonism. Symptoms which persist were mainly tremor (8) and parkinsonism or parkinson's disease (11). In 5 cases, the dose was not changed. The patient

recovered or was recovering in 4 cases and the patient did not recover in one case. In 2 cases the dose was reduced. One patient recovered and one patient did not recover. In 1 case the drug was withdrawn and the patient recovered with sequelae. In 2 cases, the action taken concerning trimetazidine is not known.

Parkinson's syndrome is already listed in the current safety information. Events and related symptoms reported with trimetazidine are rare (0.36/100,000 patient-years), in general reversible (around 80 %) and therefore manageable when the treatment is stopped. Nevertheless, in the Risk Management Plan "Parkinson's syndrome" as an identified risk was implemented.

Pharmacoepidemiological studies

No formal pharmacoepidemiological studies have been performed with trimetazidine. However, two publications from Spanish authors reported cases of Parkinson's symptoms and trimetazidine.

Firstly, a retrospective study (Marti-Masso, 2005) was carried out on 10,258 patients attending a neurological out-patient clinic between January 1990 and August 2003. Of these, 130 patients (48 males and 82 females, mean age of 63.3 years) received trimetazidine. Treatment with this drug was initiated in 57 patients for vertigo, 20 for dizziness that was probably related to anxiety, 13 for tinnitus, 10 for gait disorders, 3 for hearing loss, 3 for ischemic retinopathy and 2 for ischemic cardiopathies (unknown in 22 cases). Of the 130 patients taking trimetazidine, 56 (43%) experienced neurological adverse reactions that involved either new neurological symptoms or the worsening of a previous neurological disorder (parkinsonism: 32; gait instability: 15; tremor: 9). In all cases, withdrawal of trimetazidine improved symptoms. However, in 29 cases other drugs that were capable of inducing parkinsonism or worsening gait instability were simultaneously withdrawn.

Second, a prospective observational study (Ortin Castano, 2006) lasting one year (February 2004 to February 2005) included all new adult outpatients at a neurology ward. In a total of 685 patients, 60 neurological adverse drug events were detected: the most frequent adverse events detected were medication overuse headache (51.6%) and drug-induced parkinsonism (38.3%), especially related to trimetazidine (10 cases, 16.7%) or sulpiride (8 cases, 13.3%).

The CHMP noted that the two Spanish publications (Marti-Masso et al, 2005; Ortin Castano, 2006) provide interesting data on case-series. Retrospectively, of 10,258 patients who attended a general neurological clinic from 1990 to 2003, 130 patients received trimetazidine: 56 of them had Parkinsonism, gait instability or tremor. In all cases, trimetazidine withdrawal improved neurological symptoms (Marti-Masso, 2005). Prospectively, 685 patients intended to the neurological clinic for one year: 60 patients were diagnosed drug-induced neurological effects; including 24 patients with Parkinsonism or tremor, of which trimetazidine was involved for 11 patients. In other words, 18 % of the drug-induced neurological events observed at the clinic were attributed to trimetazidine, and 46 % of the cases of drug-induced Parkinsonism and tremor (Ortin Castano, 2006).

Dopamine receptor antagonist properties of trimetazidine have not been identified. However, trimetazidine does induce Parkinsonism. A sub-acute or chronic toxicity for dopamine neurons should merit further attention/investigation.

Literature Publications

The following cases were retrieved from published literature was also submitted on the risk of neurological serious adverts events:

Since 1998 until 2003 about 2,500-750,000 people were on trimetazidine in the Spanish Basque region. During this period a neurologist from this region reported 8 cases of parkinsonism during trimetazidine 60 mg/day given for unknown indication. Details of the patient medical history and concomitant

medications were not available. The patients were in the age group of 72-94 years and were on trimetazidine from 6-12 months before the symptoms of parkinsonism were reported. Patients complained of tremors, akinesia and gait disorders. Two patients were prescribed levodopa and carbidopa before the role of trimetazidine was suspected. No risk factors were identified. Symptoms of parkinsonism disappeared after treatment with trimetazidine was discontinued and failed to recur after treatment with levodopa and carbidopa was stopped. The diagnosis of parkinsonism has been confirmed by the neurologist (Spain, Prescrire International, 2005, Vol 14 N 76. 63).

In 2009, the French National Pharmacovigilance Committee examined data from a national study of the adverse effects of trimetazidine. The study was done in 2 phases. In phase 1, which lasted up to 30 July 2007, 46 reports of thrombocytopenia or thrombocytopenic purpura were identified. Trimetazidine was the only suspected drug in 9 of these cases. In phase 2, the authors examined the reports received up to February to March 2008. They found 319 adverse effects which included various organs of the body. The adverse effects included hematological disorders, cutaneous disorders, malaise, dizziness, vasomotor instability, headache, arterial hypotension, tinnitus, gastrointestinal disorders, hepatobiliary disorders, internal or external bleeding, cardiac adverse effects, neuropsychological disorders, electrolyte disorders and non-fatal overdose.

In the absence of information pertaining to underlying medical condition or concomitant medications, one cannot rule out alternative etiology. With a positive temporal relationship and positive dechallenge causality can be assessed as possible (France, Prescrire International, 2010, Vol 19 N 106.74).

A 91 year old female patient with a history of arterial hypertension presented with malaise several times a week associated with fall. She was treated with oral trimetazidine 35mg b.i.d for vertigo for 9 months and oral nicardipine 50mg b.i.d for arterial hypertension. She developed orthostatic hypotension, facial hypomania, bilateral bradykinesia, cogwheel rigidity, postural instability and urinary incontinence. Computerised tomography scan was normal. Trimetazidine was stopped and 2 months later the extrapyramidal symptoms resolved but orthostatic hypotension persisted. Patient remained stable for 3 years without any recurrence of extrapyramidal symptoms. Considering a positive temporal relationship and positive dechallenge causality can be assessed as possible (Sommet et al. 2005).

An 88 year old man was started on trimetazidine for visual disturbances. No medical history or concomitant medications were reported. A week after starting trimetazidine, he experienced choreiform movements in all four limbs, impaired alertness, restless legs when falling asleep, visual hallucinations and tremor. One month later, trimetazidine was discontinued. The patient recovered from all the adverse events. In the absence of information pertaining to underlying medical condition or concomitant medications, one cannot rule out alternative aetiology. With a positive temporal relationship and positive dechallenge causality can be assessed as possible (France, Prescrire International, 2009, Vol 18 N 100.69).

A 55-year-old man, with a medical history of arterial hypertension without cardiovascular complications (diagnosed due to complaints of tinnitus), Type 2 diabetes mellitus, and hypercholesterolaemia, reported both akathisia and progressively worsening restless legs with ensuing insomnia and daytime drowsiness. The patient was treated for 5 years with trimetazidine (for the tinnitus), aspirine, and hydrochlorthiazide/fosinopril (replacing hydrochlorthiazide/benazepril). Laboratory work-up showed moderately increased blood glucose and HbA1C of 6.6% (normal range 6.0%), but was otherwise normal. Neurological examination showed a parkinson syndrome (expressionless face, slowing of walking, rigidity, dysarthia). Stopping treatment with trimetazidine without changing other medication allowed for regression of symptoms within weeks. Follow-up neurological examination was normal, the patient no longer reported akathisia symptoms and slept better. The reporter concluded that this case,

seen in the light of previous case reports, justifies adding trimetazidine to the list of suspect drugs for extrapyramidal symptoms, particular parkinson syndrome.

In conclusion in all these publications, symptoms of Parkinsonism were reported after trimetazidine intake. In all cases, symptoms of Parkinsonism disappeared after trimetazidine discontinuation and in some cases symptoms failed to reappear after treatment with levodopa and carbidopa was stopped. These findings are in agreement with data provided by all MAHs.

Prevalence in exposed population and in the reference population

The prevalence of idiopathic Parkinson's disease in industrial countries is generally estimated at 0.3% of the entire population and arises to 1% in people over 60 years of age.

For the exposed population with trimetazidine (data from post-marketing surveillance), the estimated incidence rate of Parkinson's disease or related symptoms is 0.36/100,000 patient-years (PY) for all cases (161 patients). The worldwide annual incidence rate of Parkinson's disease is around 16-19/100,000 patient-years (Twelves, 2003). Although spontaneous events are underreported, the incidence rate of Parkinson's disease or related symptoms observed with trimetazidine is lower than the reported incidence rate of Parkinson's disease in the general population.

In people aged 60 or 65 years and more, the incidence of parkinsonism or parkinson's disease ranges from 183 to 557/100,000 patient-years (Perez, 2010; Taylor, 2006; Benito-Leon, 2004). The incidence increased with age.

In addition, a specific analysis of Parkinson's disease incidence rate in the reference populations (patients aged 65 years or more with symptomatic angina pectoris or with vertigo or tinnitus) was undertaken on the GPRD database. This analysis displayed a higher incidence rate of Parkinson 's disease in patients with angor (188/100,000 PY) than in the general population (141/100,000 PY) but no differences between patients with vertigo/tinnitus (164/100,000 PY) and the general population.

After trimetazidine withdrawal, most of patients recovered and the time for recovering could take several months; however some patients had partially recovered.

In summary, nervous disorders are the most frequent ADRs reported during trimetazidine treatment, of which approximately half of the cases are related to Parkinson syndromes and related disorders, which is a very unusual matter reported for a drug used in cardiology and Ear Nose and Throat.

Analysis of patients treated with trimetazidine in combination with anti-Parkinson (AP) medicinal product.

A retrospective study was designed including two cohorts of patients. A cohort of patients treated with trimetazidine during 2009 and a cohort of patients not having trimetazidine in any time of their life and matched with trimetazidine cohort based on their sex, age and profile. Each cohort was observed from January 2000 until the end of 2009. The 2009 trimetazidine cohort was followed up for an additional period until May 2011.

Antiparkinsonian drugs taken into account were drugs from European Pharmaceutical Market Research Association (EphMRA) class N04 (Antiparkinsonian drugs). Two levels of analysis are carried out, a "high end" level including all N04 drugs and a "low end" level excluding patients receiving N04 drugs with other indications than Parkinson's syndrome, unless they had a parkinsonian syndrome diagnosis or a history of a pure antiparkinsonian (AP) drug prescription.

In the results, 21,972 patients are included in 2009-trimetazidine cohort. Among them, 45.3% had a cardiovascular profile, 30.0% ENT profile, 0.4% ophthalmological profile and 24.3% had an undefined profile. Trimetazidine was mostly prescribed in women. Mean age was 69.4 years (higher in the

cardiovascular profile: 74.8 years). Females were slightly older (about 2.5 years) than men, except in the ophthalmology group.

At the low end level, 430 patients (1.96%) have been prescribed an AP drug with trimetazidine. 186 patients (43.3% of the population) had the initiation of the AP drug before trimetazidine was initiated. 163 patients (37.9%) had the initiation of the AP drug after trimetazidine was initiated. 81 patients (18.8%) had an undefined chronology.

In the high end level, 887 patients (4.04%) have been prescribed an AP drug with trimetazidine. 378 patients (37.9% of the population) had the initiation of the AP drug before trimetazidine was initiated.427 patients (48.1%) had the initiation of the AP drug after trimetazidine was initiated. 82 patients (9.2%) had an undefined chronology.

Overall, at the high or low level, these values indicate that, in patients receiving trimetazidine, there is an excess of Parkinson treatment/Parkinson disease between 0,55 % (1,96-1,41) and 1,61% (4,04-2,43) of the population. This suggests that trimetazidine treatment significantly increased the prevalence of treated Parkinson syndromes.

Analysis of a pharmacovigilance database

The pharmacovigilance data base of one MAH was analysed for neurological serious adverts events.

Out of the 1,019 patients-cases having presented an ADR with trimetazidine, 58 received an anti-Parkinsonian treatment. Among the 58 patient-cases, 33 patients received anti-parkinsonian drugs that were prescribed for treatment of an extra-pyramidal sign or symptom that had appeared under treatment with trimetazidine.

	All indications	**Patients with angina**	**ENT indication**	**OPH indication**
Number of cases since MA **Number of serious cases**	58 34	10 7	11 5	7 1
Number of fatal cases	2	0	0	0
Gender	34M / 24F	8M / 2F	5M / 6F	3M / 4F
Age				
Mean (yrs)	78.0	76.5	80.9	72.9
Min – max (yrs)	28 – 94	63 – 90	67-93	66 – 80
< 65years old	2	1	0	0
65-75 years old	16	4	2	5
75-85 years old	30	4	6	2
> 85 years old	9	1	3	0
Unknown	1	0	0	0
Occurrence of the event after the first intake of the drug				
< 3 months	3	0	1	0
3 months – 1 year	5	0	4	0
1 year – 3 years	7	2	1	2
3 years – 10 years	8	2	3	3
> 10 years	6	1	1	2
Unknown	26	5	1	0
Relevant medical history				
Parkinson's disease	14	3	3	0
Parkinsonism	1	0	1	0
Tremor	1	1	0	1
Prescription of anti-parkinsonian treatment				
Before TMZ initiation	1	1	1	0
Concomitant to TMZ	34	5	6	1
At event diagnosis	6	4	4	4
Unknown	7	1	0	2
Number of patients presenting an AE				
Parkinson syndrome	33	7	9	7
Other :	25	3	2	0

Hypotension/orthostatic hypotension hallucination	6 3			

In summary the MAH argued that this analysis showed that initiation of an antiparkinsonian drug for parkinsonian symptoms linked to trimetazidine is rare (3.2 % of the 1019 total reported cases).

The CHMP noted that within the pharmacovigilance database, no control group is available. However, the fact that 3.2% of patients receiving trimetazidine and having adverse reactions, were initiated with antiparkinson drug, suggested an increased clinically significant risk due to trimetazidine. Prevalence of treated Parkinson disease in the population is less than 0.5 % for patients less than 64 years old, around 0.7 % for patients aged 65-69 years old and 1.1 % for patients aged 70-74 years old which confirms that there is an increased clinically significant risk due to TMZ. The maximal prevalence occurs in the group 80-85 years old, which stays below 3 %.

Hypotension

Fifty eight patient-cases (58 events) were collected cumulatively from the first marketing authorisation of trimetazidine until May 29, 2011 representing an incidence of 0.13/100,000 patient-years.

Out of the 58 cases, 44 (75.9%) were considered as serious; one patient died in a context of hepatocellular failure, orthostatic hypotension was reported in 34 cases (58.6%), including 30 serious cases. In 22 cases, orthostatic hypotension was associated with dizziness (1 case), malaise (1case) or fall (21 cases). Among the 29 cases of orthostatic hypotension with a known outcome, 28 cases recovered: 26 cases after stopping trimetazidine, 1 case recovered while trimetazidine treatment was maintained, while in 1 case, the action taken regarding the study drug was unknown at the time of reporting, out of the 49 patients, for whom the outcome was known, 48 cases recovered or recovering: 39 cases after stopping trimetazidine, 2 cases recovered while trimetazidine treatment was maintained, while in 2 cases, the action taken regarding the study drug was unknown at the time of reporting; the remaining 5 cases occurred in a context of overdose, of incorrect dose administered, medication error or drug dispensing error, in only 5 cases, trimetazidine was reported without any concomitant treatment.

The analysis of the cases showed that hypotension concerned more frequently women (74.1%) and patients older than 75 years (74.1%), and in most of the cases, patients received trimetazidine in combination with drugs for which this reaction has been described (79.3%) and/or had a relevant medical history (48.3%; hypertension: 23; arrhythmia: 9; cardiac failure: 5; hypotension: 1).

Orthostatic hypotension is already listed in the current safety information. Overall, the analysis of the reports of hypotension did not provide any new safety signal. In the risk management plan (RMP) 'orthostatic hypotension' as an identified risk was implemented.

Thrombocytopenia

Sixty nine (69) patient-cases (70 events) were collected cumulatively from the first marketing authorisation of trimetazidine until May 29, 2011 representing an incidence of 0.16/100,000 patient-years.

Out of the 69 cases, 43 were serious, including 2 fatal cases in a context of infection and renal failure and in a context of brain haemorrhage. In most cases, patients received trimetazidine in combination with drugs for which this reaction has been described (73.9%) and/or had a medical history which could favour such events (14.5%). Out of the 53 patients, for whom the outcome was known, 46 cases recovered: 35 cases after stopping trimetazidine, 4 cases recovered while trimetazidine treatment was

maintained, while in 6 cases, the action taken regarding the study drug was unknown at the time of reporting. In one case, thrombocytopenia occurred 8 days after stopping trimetazidine.

Thrombocytopenia is not a listed event in the current safety information. Based on the number of events and their seriousness, it is proposed to implement a Risk Management Plan (RMP) with 'thrombocytopenia' as a potential risk. The CHMP agreed that from the submitted data, the causality of trimetazidine cannot be excluded and is of concern. The section 4.8 of the SmPC should be updated as well as the RMP.

Agranulocytosis - leukopenia - neutropenia

Thirty-three (33) patient-cases (37 events) were collected cumulatively from the first marketing authorisation of trimetazidine until May 29, 2011 representing an incidence of 0.07/100,000 patient-years as compared to the incidence rate reported from literature (0.92/100,000 patient-years). Out of the 33 reports, 31 were serious, including 2 fatal cases, both in a context of infection. In most of the cases, patients received trimetazidine in combination with concomitant drugs for which this reaction has been described (87.9%) and/or presented a relevant medical history of similar reactions (27.3%).

In 3 cases, the action taken regarding the study drug was unknown at the time of reporting,

Agranulocytosis is not listed in the current safety information. Based on the number of events and their seriousness, it is proposed to implement a Risk Management Plan with 'Agranulocytosis' as a potential risk.

The CHMP agreed that the causality of TMZ in the occurrence of agranulocytosis, leukopenia and neutropenia cannot be excluded and is of concern. The section 4.8 of the SmPC should be updated as well as the RMP.

2.3.1. Discussion on safety

Since the marketing authorisation, 161 cases of Parkinson syndrome and related symptoms have been collected with trimetazidine until May 29, 2011, representing an incidence of 0.36/100,000 patient-year (PY). Among them, 67 cases (88 events) were considered as serious, representing an incidence of 0.15/100,000 PY. Overall, cases were more frequently reported in female patients (62.1%) and a total of 80% of patients were older than 65 years. The most exposed population based on sales data, is patients aged more than 75 years old.

It is important to note that a relationship between parkinsonian symptoms and trimetazidine treatment is very difficult to be established, given that the product is indicated in an elderly population where Parkinson syndrome is frequently observed. However, data on the co-prescription of antiparkinson drugs with trimetazidine (IMS study) support the evidence of an association of trimetazidine with parkinsonian symptoms. In addition the positive dechallenge of parkinsonian symptoms after the only withdrawal of trimetazidine, and the positive rechallenge further support the existence of a risk of parkinsonian symptoms associated with trimetazidine.

The highest reported incidence was observed in France in 2008 and was estimated at less than 2/100,000 treated-patients (the number of patients treated in France in 2008 was greater than one million). Thus, considering the reporting rate from post-marketing experience, Parkinson's syndrome and related symptoms with trimetazidine appears to have a low prevalence.

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.

This review was based on information available from clinical reports. Cases reported by the neurologists in the literature were all considered as Parkinsonism with a plausible relationship with trimetazidine. Overall, 70 cases of Parkinson's syndrome were assessed for which a relationship to trimetazidine cannot be excluded (plausible, 51 cases) or was doubtful (19 cases). The analysis of the 51 plausible cases confirmed that symptoms are reversible after treatment discontinuation. The majority of the patients who recovered, had their symptoms disappeared within 4 months after trimetazidine withdrawal. However, other patients had symptoms only partially reversible after trimetazidine withdrawal. Considering all the currently available data the CHMP concluded that the 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 pakinsonian symptoms and tremors.

The Emeriau PK study has shown high plasma concentrations of trimetazidine in old patients, receiving the usual dose of 35 mg x 2/day. Renal impairment plays a major role by decreasing trimetazidine elimination. 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 frequently in treated elderly patients with high trimetazidine plasma concentrations. 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 requested by the CHMP to investigate the effects of renal impairment and age on the trimetazidine safety profile.

Considering all the 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 have been included in the risk management plan (RMP) and reflected in the relative sections of the SmPC.

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.

2.4. Risk management plan

The CHMP discussed the risk management plans which have been submitted by some MAHs.

Summary of the additional safety concerns on the risk management plan

During the CHMP assessment RMPs were submitted by MAHs. The CHMP noted that Parkinson's syndrome is already listed in the current safety information. Events and related symptoms reported with trimetazidine are rare (0.36/100,000 patient-years), in general reversible (around 80 %) and therefore easily manageable when the treatment is stopped. Nevertheless, in the Risk Management Plan 'Parkinson's syndrome' as an identified risk needs to be implemented.

Orthostatic hypotension is already listed in the current safety information. Overall, the analysis of the reports of hypotension did not provide any new safety signal. In the Risk Management Plan 'Hypotension' as an identified risk was implemented.

Some new potential, very rare and reversible adverse effects were highlighted during the referral procedure, including trombocytopenia, agranulocytosis and liver dysfunction have been included in the

RMP. In particular agranulocytosis is not listed in the current safety information. Based on the number of events and their seriousness, it is proposed to implement a Risk Management Plan with 'agranulocytosis' as a potential risk.

The CHMP, having considered the data submitted is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product:

Communication to healthcare professionals is to be distributed regarding the amended indication for the trimetazidine-containing products on angina pectoris and the deletion of the indications on otology and ophthalmology.

In addition future studies need to be performed on the safety of the products, notably on the pharmacokinetic effects of renal impaired patients and elderly, a drug utilization study assessing the impact of the risk minimization measures on the prescription of the products and a PASS study on the Parkinson events and the EPS relation.

In addition a proposal for a specific questionnaire to be used for documenting all notified cases with symptoms related to Parkinsonism was provided and agreed by the CHMP.

2.5. Overall conclusions and benefit/risk assessment

EFFICACY

Angina pectoris

The clinical trials have been performed over thirty years. However a sufficient number of more recent trials provide adequate evidence of the efficacy of TMZ as add-on therapy in the treatment of angina pectoris.

The clinical program for TMZ in this indication included studies mainly conducted with the 20 mg dosage; however, all results also applied for the 35 mg modified release (MR) formulation as the only difference between both dosages is the number of daily intakes, the bioavailability being similar. The submitted data are mainly based on literature publications, some clinical reports have been provided.

Pre-clinical and clinical data show that TMZ improves myocardial ischemia in patients with coronary artery disease and therefore ameliorates angina pectoris through the improvement of the production of myocardial high energy phosphates. The mechanism of action of trimetazidine is such that the drug is devoid of any effect on heart rate or blood pressure.

TMZ has been tested against placebo or active comparator, in monotherapy or in combination with reference treatments such as beta blockers or calcium-channel blockers. The population included in the clinical program can be considered representative of the target population suffering from angina pectoris. The main set of data in support of the add-on indication of trimetazidine in symptomatic patients with angina are derived from the TRIMPOL-II study (2001), the study by Sellier (2003) and the revised data from the VASCO study (2011). 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).

The TRIMPOL-II showed that trimetazidine significantly improves exercise capacity and exercise-induced myocardial ischemia when added to metoprolol. The efficacy was confirmed in patients at maximal dose of metoprolol as well as in patients with recurrent angina.

The Sellier study showed a statistically significant difference on the primary outcome, time to 1-mm ST-segment depression, in favour of trimetazidine when the drug is added to atenolol. It is considered that the study should be considered adequate to show the efficacy of trimetazidine only with reference to the primary endpoint.

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: total exercise duration +23.8 s versus +13.1s ($p=0.01$) and time to onset of angina +46.3 s versus +32.5 s ($p=0.005$). 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 CHMP considers that the revised indication as proposed is in line with the scientific evidence available at present for trimetazidine and it is supported by trials 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 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 in monotherapy due to haemodynamic intolerance or chronotropic incompetence.

Concerns were however raised for the lack of long-term safety and efficacy data deriving from large studies designed according to current EMA guidelines. In this regard, the proposed multicentre, randomised, double-bind, placebo controlled long-term study to evaluate in post-PCI patients and the prospective cohort studies are considered adequate to assess the long term efficacy and safety of trimetazidine for the prevention of angina pectoris and the prevalence of the very rare adverse events like extrapyramidal symptoms (EPS), and are considered necessary for the confirmation the long-term efficacy and safety of the product.

Otology - Ear, Nose, 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 otology (ENT) indications, 10 clinical studies were submitted or presented as literature references. These studies aimed at demonstrating a clinical benefit of trimetazidine in the treatment of tinnitus and/or dizziness and/or hearing loss which indications overall correspond to the wording of the registered indications in Europe.

Nine 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 if treatment

(between 2 and 3 months) not in line with what is required by these pathologies that necessitate long term treatments.

Most ENT trimetazidine clinical trials have been conducted with the 20 mg dosage. In some studies the dosages used are lower (40 mg/day) than those recommended in the marketing authorisation (60 mg/day or 70 mg/day), which is also a limit of these studies in terms of safety of use.

Among these studies, five old 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 symptomatologies 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 (conducted in 1984/1990) whereby the results are disputable 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 firstly suggested. Three studies were conducted against betahistine (Haguenauer, 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 do not conclude on the demonstration of a relevant clinical benefit for patients suffering from tinnitus, dizziness or hearing loss and receiving trimetazidine.

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 properties suggested limited methodology in the ENT field and do not confirm the current methodology of investigation 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 in its ophthalmologic indications, nine clinical studies were submitted. 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 dosage 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.

In addition among these nine studies, three were non-comparative studies; three were comparative studies of short duration (up to 3 months) conducted against reference products chosen at the time of these studies that, finally, are no more considered as therapies of choice to treat or prevent retinal or glaucoma diseases (i.e. cinnarizine, piridoxilate etc.) by the community of ophthalmologists; two were studies conducted against placebo which included a small number of patients (n=32 and n=242) presenting multiple symptomatologies with a monitoring of a maximum of 6 months duration, which is insufficient for slow progressing pathologies.

The three, studies of short duration (up to 3 months) conducted against reference products of the time (e.g. cinnarizine, piridoxilate). Furthermore, these studies present other specific weaknesses.

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 symptomatic treatment of vertigo and tinnitus. 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 pakinsonian 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 frequently in treated elderly patients with high trimetazidine plasma concentrations. The Emeriau PK stud 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 trombocytopenia, 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-bind, placebo controlled long-term study to evaluate in post-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.

Benefit –risk balance

On the basis of all available evidence, the CHMP 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 anti-angina 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 symptomatic treatment of tinnitus, vertigo and visual field

disturbances, the CHMP concluded that in view of the updated safety profile the benefits no longer outweigh the risks and these uses should no longer be authorised.

2.6. Communication plan

As part of this referral procedure the CHMP agreed the wording of a Direct healthcare professional communication (DHPC) designed to inform prescribers of the new angina pectoris indication and the deletion of the ENT and ophthalmologic indications. In addition the information on the contraindicated use of the products in patients with renal impairment or Parkinsonian symptoms is highlighted. This communication is to be sent within 30 days after commission decision to all relevant healthcare professionals.

2.7. Changes to the product information

A. Summary of Products Characteristics

Section 4.1 Therapeutic indications

The new proposed indication is as follows:

> *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.*

Section 4.2 Posology and method of administration

The posology in special populations as elderly and renal impaired patients has been clarified in this section of the SmPC.

Section 4.3 Contraindications

The CHMP concluded that the products should not be used in patients with Parkinson disease, parkinsonian symptoms, tremors, restless leg syndrome, and other related movement disorders or with severe renal impairment (creatinine clearance < 30ml/min).

Section 4.4 Special warnings and precautions for use

The CHMP also recommended for warnings to be included in this section. 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 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. Falls may occur, related to gait instability or hypotension, in particular in patients taking antihypertensive treatment. Caution should be exercised when prescribing trimetazidine to patients in whom an increased exposure is expected i.e. moderate renal impairment and elderly patients older than 75 years old.

Section 4.8 Undesirable effects

This section was amended to include the new adverse events of Parkinsonian symptoms (tremor, akinesia, hypertonia), gait instability, restless leg syndrome and other related movement disorders,

arterial hypotension have been added. Blood and lymphatic system disorders agranulocytosis, thrombocytopenia, thrombocytopenic purpura have been added. Hepatitis has also been added.

Section 5.1 Pharmacodynamic properties

The mechanism of action was clarified in this section. In addition data from efficacy and safety studies have been added.

B. Package Leaflet

The package leaflet was aligned to the SmPC proposals.

3. Overall conclusion

Having considered the overall submitted data provided by the MAHs in writing and in the oral explanations, the CHMP concluded 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 symptomatic treatment of tinnitus, vertigo and visual field disturbances, the CHMP concluded that in view of the safety profile and of the limited evidence of efficacy the benefits no longer outweigh the risks and these uses should no longer be authorised.

The Committee also 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 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 incidence and are usually reversible after treatment discontinuation. Caution should be exercised when prescribing trimetazidine to patients in whom an increased exposure is expected moderate renal impairment, elderly patients older than 75 years old.

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

The CHMP also agreed that a study to assess the effect of renal impairment and age on trimetazidine pharmacokinetics need to be conducted. A 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.

The Committee overall 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.

Therefore, the CHMP recommended the variation to the terms of the marketing authorisations for the medicinal products referred to in Annex I

The conditions affecting the marketing authorisations are set out in Annex IV to the opinion.

The divergent positions are appended to this assessment report.

Appendix 1

Divergent positions

Article 31 referral of Directive 2001/83/EC

Procedure No: EMEA/H/A-31/1305

Trimetazidine containing medicinal products

Divergent statement

Trimetazidine is a piperazine derivative, presented as a metabolic agent, claimed to protect against ischemia by increasing glucose metabolism relative to that of fatty acids.

In April 2011, France triggered the current Article 31 referral to assess the risks and the benefit of trimetazidine for all authorised dosages and indications after the negative opinion given by the French National Advisory Board on the benefit/risk ratio of trimetazidine-containing medicinal. The negative opinion was based on morbidity associated with adverse effects (especially Parkinson syndromes) together with insufficient evidence of significant efficacy from well-conducted clinical trials.

Trimetazidine-containing medicinal products have been indicated in European Union for the treatment of: i) prophylactic treatment of angina pectoris crisis ; ii) ancillary symptomatic treatment of vertigo and tinnitus and iii) ancillary treatment of visual acuity decrease and visual field disturbances due to vascular reasons. CHMP agreed to reject the ophthalmologic and vertigo/tinnitus indications due to the absence of demonstration of any relevant therapeutic benefit but to retain a second line indication for angina treatment in patients remaining symptomatic despite treatment with conventional first line anti-anginal drugs.

Regarding the indication in the treatment of angina pectoris, based on the overall data submitted (clinical trials and meta-analysis), the previous indication "*prophylactic treatment of angina pectoris crisis"* is not supported by sufficient clinical data to be maintained. Indeed, the largest trial, the VASCO study, showed that trimetazidine as an add-on treatment to atenolol did not improve exercise capacity (the main endpoint) or ischemic threshold during exercise ***(time to onset of 1mm ST and time to onset angina)*** in coronary patients (70 mg/d or 140 mg/d). In the other clinical studies, improvement of exercise capacity or angina threshold during exercise was inconsistently observed and when observed, the amplitude of effects was of a too small magnitude (few seconds compared with placebo) to translate into a relevant clinical benefit.

The newly proposed indication "*Trimetazidine is indicated 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*" is not supported by sufficient convincing and relevant clinical data to be approved. This new restricted indication is only based on post-hoc subgroup analyses (symptomatic patients) of the non-conclusive results of the add-on VASCO study and the add-on Sellier (2003) study (non conclusive in the ITT population).

Lastly, a new clinical trial in post-PCI patients as proposed by the MAH would be considered necessary to further substantiate efficacy and safety in this population. but serious doubts are raised concerning the feasibility of this clinical trial to provide such information in a reasonable time frame.

The main identified serious risk is related to Parkinson syndrome and related symptoms. Trimetazidine can cause or worsen parkinsonian symptoms (tremor, akinesia, hypertonia) and the frequency of these adverse effects is unknown and likely underreported in an elderly patient population, which prevents to reliably assess its frequency. The true magnitude of this risk remains unknown and is probably underestimated.

Some other adverse effects are reported with trimetazidine and they can contribute to a higher morbidity. This includes cases of fall, hypotension, vertigo, insomnia and other neurological effects. In addition, the review of the safety information accumulated during the post-marketing period has enlarged the original safety profile of trimetazidine to include some new potential adverse effects, including trombocytopenia, agranulocytosis and hepatitis that, although rare or very rare and largely reversible after drug discontinuation, may be potentially severe.

Overall, for these reasons, we consider that the benefit/risk ratio is negative in all indications.

CHMP members expressing a divergent opinion:

Pierre Demolis (FR)	21 June 2012	Signature: …….....
Robert James Hemmings (UK)	21 June 2012	Signature: …….....
Rafe Suvarna (UK)	21 June 2012	Signature: …….....
Alar Irs (EE)	21 June 2012	Signature: …….....
Andrea Laslop (AT)	21 June 2012	Signature: …….....
Jan Mueller-Berghaus (DE)	21 June 2012	Signature: …….....
Harald Enzmann (DE)	21 June 2012	Signature: …….....
Romaldas Mačiulaitis (LT)	21 June 2012	Signature: …….....
John Joseph Borg (MT)	21 June 2012	Signature: …….....