



HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

14 September 2011

VASTAREL 20 mg, film-coated tablet

B/60 (CIP code: 322 050-6)

B/100 (CIP code: 322 051-2)

VASTAREL 20 mg/ml, oral solution, drops

1 vial of 60 ml (CIP code: 322 752-0)

VASTAREL 35 mg, modified-release film-coated tablet

B/60 (CIP code: 357 245-8)

B/100 (CIP code: 357 247-0)

Applicant: SERVIER

Trimetazidine (dihydrochloride)

ATC code: C01EB15

List II

Dates of Marketing Authorisations:

VASTAREL 20 mg, film-coated tablet: 30/03/1978

VASTAREL 20 mg/ml, oral solution, drops: 02/05/1979

VASTAREL 35 mg, modified-release film-coated tablet: 06/08/2001

Reason for request: Reassessment of actual benefit (AB) in compliance with article R-163-21 of the French Social Security Code.

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Trimetazidine (dihydrochloride)

1.2. Indications

- Prophylactic treatment of angina pectoris attacks
- Adjunct symptomatic treatment for vertigo and tinnitus
- Adjunct treatment for reduced vision and visual field disturbances of presumed vascular origin.
- ***As the actual benefit (AB) of Trimetazidine in this indication had been judged insufficient at the time of the reassessment performed in 2006, this indication will not be analysed again in this opinion.***

1.3. Dosage

“One 20 mg tablet three times per day or one 35 mg tablet in the mornings and in the evenings or 3 ml (60 drops) in three intakes, at mealtimes.

The benefit of the treatment should be reassessed after three months and trimetazidine should be withdrawn in the absence of any response.

This medicinal product should not be used in children or adolescents given the lack of safety and efficacy data.”

2 REMINDER OF THE COMMITTEE'S OPINIONS AND CONDITIONS OF INCLUSION

Opinion of the Committee of 6 November 1996 (Vastarel 20 mg tablet and oral solution)

In its ENT indication, Vastarel has a symptomatic effect. It has a degree of usefulness in the treatment strategy for vertigo and tinnitus. In light of its actual benefit, covering the cost of Vastarel is justified.

Opinion of the Committee of 14 February 2001 (Vastarel 20 mg tablet and oral solution) – Reassessment of actual benefit (AB)

The actual benefit in this indication is moderate.

Opinion of the Committee of 15 May 2002 (Vastarel 35 mg)

The actual benefit of Vastarel 35 mg is moderate in the adjunct symptomatic treatment of vertigo and tinnitus.

No new clinical data are provided by the applicant.

Level of improvement in actual benefit (IAB): this is an extension of the product spectrum that offers no improvement in actual benefit (IAB V).

**Opinion of the Committee of 26 March 2003
(Vastarel 20 mg tablet and oral solution) – Reassessment of actual benefit (AB)**

Actual benefit: moderate.

**Opinion of the Committee of 5 July 2006 – Reassessment of the actual benefit in the indication
“Adjunct treatment for reduced vision and visual field disturbances of presumed vascular
origin”**

Actual benefit: insufficient.

**Opinion of the Committee of 28 March 2007 – Reassessment of the actual benefit in the
indication “Adjunct symptomatic treatment for vertigo and tinnitus”**

Actual benefit: low.

Opinion of the Committee of 5 December 2007 – Renewal of inclusion

Prophylactic treatment of angina pectoris attacks: moderate actual benefit.

Adjunct symptomatic treatment for vertigo and tinnitus: low actual benefit.

Adjunct treatment for reduced vision and visual field disturbances of presumed vascular origin: insufficient actual benefit.

3 SIMILAR MEDICINAL PRODUCTS

3.1. ATC Classification

C : cardiovascular system
C01 : cardiac therapy
C01E : other cardiac preparations
C01EB : other cardiac preparations
C01EB15 : trimetazidine

3.2. Medicines in the same therapeutic category

Stable angina indication:

RANEXA, ranolazine

3.3. Medicines with a similar therapeutic aim

Stable angina indication:

These are the other medicinal products indicated in the management of stable angina: beta-blockers, calcium channel inhibitors, long-acting nitrate derivatives, nicorandil: (ADANCOR, IKOREL and generics), ivabradine (PROCORALAN), molsidomine (CORVASAL and generics).

Dizziness and tinnitus indication:

These are the other proprietary medicinal products indicated in dizziness:

- acetylleucine: TANGANIL
- betahistine: SERC, BETASERC, EXTOVYL, LECTIL
- meclozine: AGYRAX

Peripheral vasodilators:

- ginkgo biloba: TANAKAN, TRAMISAL, GINKOGONK
- piracetam: AXONYL, GABACET, NOOTROPYL

4 ANALYSIS OF AVAILABLE DATA

In 2005, an initial national pharmacovigilance survey, devoted to Parkinsonian syndromes, was conducted and led to changes being introduced to the “Undesirable effects” section of the SCP for VASTAREL, including the addition of the onset of Parkinsonian symptoms.

The national pharmacovigilance survey initiated in 2007 led to changes to the “Special warnings and precautions for use” section of the SCP with the addition of a reference to the fact that trimetazidine could exacerbate or induce symptoms of Parkinsonism, or lead to falls due to arterial hypotension or a postural instability; trimetazidine has therefore been included in List II of poisonous substances.

The pharmacovigilance survey was continued and, in early 2010, Afssaps decided to reassess the benefit/risk ratio for this medicinal product in its three indications.

This reassessment was done and on the occasion of the MA Committee meeting of 7 April 2011 its members voted “against keeping trimetazidine on the market” in its three indications, accompanied by a request for reassessment at European level (Article 31). The EMA started this reassessment on 19 May 2011 and an initial list of questions was sent to the company, which replied on 29 August 2011. The EMA’s conclusions are expected in the final quarter of 2011.

4.1. Efficacy

Only the clinical data relating to the indications validated by the MA will be taken into account in this opinion.

In consequence, the meta-analyses by Gutierrez 2008 and Gao 2011, which were particularly focused on heart failure patients, will not be developed in this opinion.

4.1.1. Stable angina

a. Summary of the clinical data described in the opinion on registration (35 mg) of 15 May 2002

“One clinical trial based on a standardised exercise tolerance test carried out 12 hours after taking VASTAREL 35 mg or a placebo in a population otherwise receiving a background treatment with a beta-blocker. This randomised study shows a statistically significant prolongation of the time to onset of ST-segment depression.

There are no known serious adverse effects, including in elderly subjects.

This placebo-controlled study establishes the anti-ischaemic efficacy of trimetazidine 35 mg (VASTAREL 35 mg) 12 hours after administration, which allows a dosage of two intakes per day”

b. New clinical data

VASCO 2008 study (unpublished report)

The objective of this randomised, double-blind, comparative study was to assess the efficacy and safety of two dosages of VASTAREL (70 and 140 mg per day) in combination with atenolol 50 mg/day versus placebo in 1962 patients with stable angina previously treated with atenolol* 50 mg/day followed up for 12 weeks.

* *The dose of atenolol used in this study is not optimal; in fact, the atenolol dose validated by the MA in the indication "Prophylaxis of angina attacks" ranges from 100 to 200 mg per day.*

Inclusion criteria: Patients with stable angina for at least 3 months (class II or III according to the classification of the Canadian Cardiovascular Society – CCS) and two stable (variation < 20%) positive exercise tolerance tests (ETTs) (walking on a treadmill following the Bruce protocol).

The age of the included patients was determined according to their comorbidities: Patients aged 30 to 80 years with confirmed coronary artery disease¹ and men aged 40 to 80 years and women aged 60 to 80 years with an undocumented coronary artery disease.

Treatments:

- VASTAREL 70 mg/day, n = 654,
- VASTAREL 140 mg/day, n = 655,
- placebo n = 653.

Primary efficacy endpoint: variation in the total exercise duration (TED) after 12 weeks of treatment, assessed by means of an exercise tolerance test on a treadmill in accordance with the Bruce protocol (cf. appendix).

RESULTS: intention-to-treat analysis

On inclusion, the average number of angina attacks was slightly lower in the group on trimetazidine 70 mg/day (2.8 ± 3.9) than in the group on 140 mg/day (3.2 ± 4.9) and the placebo group (3.3 ± 4.9).

After 12 weeks of treatment, no significant difference in terms of total exercise duration was observed between trimetazidine 70 mg/day and 140 mg/day and the placebo: 17.2 ± 65.2 versus 21.9 ± 72.4 versus 15.9 ± 67.6 , NS.

Cochrane meta-analysis²

A Cochrane review, which included 23 randomised, double-blind placebo-controlled clinical studies involving a total of 1378 patients with stable angina, followed up for an average of 8 weeks, was published in 2005.

Authors' conclusions: "This meta-analysis confirms the modest efficacy of trimetazidine in the treatment of stable angina, by comparison with the placebo."

In light of the VASCO publication, the company produced an update of the Cochrane review, including in particular the results of this study cited above.

RESULTS: In all, 27 studies were included, comprising a total of 2713 patients.

An improvement in the total exercise duration of 23.31 seconds [2.65; 43.97] was observed with trimetazidine by comparison with the placebo.

¹ confirmed coronary artery disease defined by an antecedent of myocardial infarction > 3 months and/or coronary revascularisation > 6 months and/or stenosis $\geq 50\%$ of a major coronary artery.

² Ciapponi A et al. Trimetazidine for stable angina. The Cochrane collaboration 31 May 2005.

The level of evidence of these results remains low, especially taking into account the factors below:

- *Insufficient quality of the studies performed*: the trials were for the most part old, with small populations, using variable methodologies not conform to European guidelines (ITT analyses often not available, failure to take into account the multiplicity of the analyses, primary endpoints not defined a priori),
- *Intermediate nature of the efficacy endpoints considered*,
- *High probability of publication bias*, to the extent that the trials were carried out before the Good Clinical Practice guidelines were drawn up in 1987 and before the introduction in 1988 of the law protecting persons involved in biomedical research (Huriet Law), and before the obligation to declare a protocol when proposing to carry out a study.

- *Intertrial heterogeneity*:
 - just one trial shows a very substantial difference in favour of trimetazidine, raising the question of the reliability of the results,
 - the results of the two trials relating to the 35 mg dosage are not conclusive,
 - lastly, the more recent the studies, the less significant their results appear to be.

Networked meta-analysis

This unpublished networked meta-analysis was carried out by the applicant under the control of two experts (Prof. Danchin and Prof. Grouin).

RESULTS:

This meta-analysis shows an absence of difference between trimetazidine and the other antianginal agents investigated (dihydropyridines, nitrate derivatives, nicorandil, ranolazine) in terms of the ergometric parameters and the symptomatology (prevention of angina attacks and consumption of fast-acting trinitrine).

The level of evidence of these results remains low, especially taking into account the factors below:

- the decision to a priori exclude bradycardia-inducing drugs (in particular beta-blockers) from the meta-analysis, even on the basis of regulatory considerations, remains questionable.
- the analysis of the quality of the trials finally included does not provide the Jadad score for each trial in parallel groups.
- the sensitivity analysis was carried out on just one criterion: the experimental design of the trials with systematic inclusion/exclusion of all crossover trials.
- the a priori choice of a method with random effects seems to indicate a heterogeneity frequently encountered with therapeutic effects. Unfortunately, the report does not detail this heterogeneity for each compound and each efficacy endpoint considered. One might have wished for in each case a more detailed exploration of the potential causes of the observed heterogeneity (especially as no *descriptive synthesis* of the clinical disparity between the trials has formally been carried out, even if there are summary tables included at the back of the report).
- no outline of the network of all the comparisons performed in this meta-analysis is available in the report.

Conclusions about the new data

In the VASCO study, after 12 weeks of treatment, no significant difference in terms of total exercise duration was observed between trimetazidine 70 mg/day and 140 mg/day and the placebo: 17.2 ± 65.2 versus 21.9 ± 72.4 versus 15.9 ± 67.6 , NS.

The level of evidence in the meta-analyses provided is low, given the age of the included trials, the generally inconclusive nature of their results, the nature of the efficacy endpoints considered, and the short follow-up periods.

For this reason, despite the statistically significant results, from these meta-analyses it is not possible to come to any conclusion as to the clinical relevance of the size of the observed effect.

Given the uncertainties in terms of efficacy, the adverse effects observed with trimetazidine must necessarily be taken into account when assessing this compound.

c. Conclusions of the MA Committee of 07/04/2011

“In cardiology, trimetazidine is indicated in the treatment of angina pectoris. For this indication we do have preclinical data – data on safety, prescription data – the protocol of a pharmacokinetic study based on age and kidney function, and clinical data issued from meta-analyses and from the VASCO study requested by the Committee some years ago now. (...)

This clinical study was presented in 2008 (...). According to the opinion of methodologists, this study is of excellent quality. Its results, on the other hand, are disappointing. The results obtained for the primary efficacy endpoint are not significant, the total exercise tolerance test duration being extended by only 17.2 seconds at the 70 mg dosage.

Three meta-analyses have been provided since 2008. They have been updated with the data from the VASCO study. (...)

The cardiology group considered that the VASCO study was far superior to the others on account of its quality. It finds that the efficacy of trimetazidine in the treatment of angina pectoris is too modest, or even unproven, at the strongest dosage – 140 mg per day – and the neurological side effects, in elderly patients in particular, are by no means insignificant. It requested that thought be given to the efficacy and safety of other treatments for angina other than beta-blockers.”

4.1.2. Vertigo and tinnitus

1. Summary of the data available when assessing VASTAREL in its indication “vertigo and tinnitus” (opinion of the Transparency Committee from 28 March 2007)

The company has added to the file five clinical studies^{3,4,5,6,7} already analysed by the Transparency Committee. They are therefore not dealt with in detail in this opinion.

Two new clinical studies conducted since the last opinion have been provided:

- An unpublished study assessing the efficacy of trimetazidine 35 mg versus placebo on the development of the auditory deficit in patients with presbycusis (Etude France Cochlée). This is an off-label indication for these proprietary medicinal products. This study will not be dealt with in detail in this opinion.
- The VITTE study,⁸ assessing the efficacy of trimetazidine 35 mg versus placebo in patients with peripheral vestibular disorders, which showed the efficacy of trimetazidine 35 mg on the overall EquiTest score and on the C5 criterion (vestibular component of the tests) in patients with peripheral vestibular disorders.

The efficacy of trimetazidine 35 mg is not significantly higher than placebo as regards the

³ Wayoff. Double-blind trial of trimetazidine versus placebo in cochleovestibular disease. *Sem Hop Paris* 1984; 60: 2729 - 2739.

⁴ Kluyskens et al. Trimetazidine versus betahistine in vestibular vertigo. Double-blind study. *Drugs Today* 1990; 26: 13-22.

⁵ Martini et al. Trimetazidine versus betahistine in Menière's disease. Double-blind study. *Drugs Today* 1990; 26: 23-31.

⁶ Morgon et al. Trimetazidine and tinnitus: results of multicenter hospital study. *Journal d'ORL* 1988: 30-35.

⁷ Haguenaer et al. Trimetazidine and degenerative deafness. Effects on hearing and integration. *Ann Otolaryngol Chir Cervicofac* 1990; 107: 51-56.

⁸ Vitte E, Semont A, Paolino M, Pennaforte S. Assessment of vastarel 35 mg in patients with peripheral vestibular disorder: double-blind placebo-controlled study using the EquiTest as evaluation criterion. *JF ORL*, 2002; 51 (5): 2-7.

C6 criterion, the second vestibular component of the test.

The Transparency Committee points out that the indication “peripheral vestibular disorders” does not correspond precisely to the indication “adjunct symptomatic treatment for vertigo”.

2. New clinical data

The applicant supplied the same clinical data as those mentioned in the opinion of 28 March 2007 referred to above.

The (unpublished) Sterkers 2001 study has also been mentioned; this study, which decided on the endpoints to be used and the number of subjects needed, does not come to any conclusion on the efficacy of trimetazidine. Consequently, it will not be dealt with in this opinion.

Lastly, the applicant has submitted the documents of its response to the CHMP of 29 August 2009 as part of the procedure for the reassessment of trimetazidine's benefit/risk ratio (Article 31); this document consists of a re-analysis of the above-mentioned clinical data.

3. Conclusions of the MA Committee of 04/07/2011

“For the indication relative to the treatment of vertigo, we have in addition three studies available versus the comparator betahistine. However, these studies are not defined as studies of the non inferiority of trimetazidine in relation to this comparator. The study relating to presbycusis was forwarded to the Agency because the applicant is obliged, when a benefit/risk ratio reassessment is being carried out, to let the Agency have all the available efficacy data. This study has shown no difference for the primary efficacy endpoint.

The Pneumology, Ophthalmology and ENT group issued an unfavourable opinion on keeping the indication for trimetazidine in ENT, concluding that *“it is not possible on the basis of the ENT clinical studies to demonstrate a clinical benefit for trimetazidine in the indication of adjunct symptomatic treatment for vertigo and tinnitus”*. It points to major methodological defects and considers that *“seven of the eight studies no longer meet the requirements and efficacy endpoints established in these conditions, nor the methodology currently required for a demonstration of efficacy”*. Moreover, given that in ENT trimetazidine is prescribed to elderly patients at the maximum dose and for a long period, its adverse effects are not inconsiderable.”

4.2. Adverse effects

1. Data from the latest Periodic Safety Update Reports (PSUR)

According to the data sent by the applicant, since the market launch, worldwide exposure to VASTAREL is estimated at 503 million patient-months, including 218 million patient-months in France.

The most recent PSURs available cover the period from 7 February 2006 to 1 August 2010:

- In the three-yearly PSUR (7 February 2006 to 6 February 2009), patient exposure is estimated at 141 million patient-months. During this period, 180 cases were reported, 82.2% of them in France,
- In the addendum covering the period from 7 February 2009 to 1 August 2010, there were 108 reported cases, 85 of them in France, including 13 cases of gastrointestinal disturbances, 16 falls, 16 Parkinsonian symptoms and 10 orthostatic hypotensions.

2. Conclusions of the National Pharmacovigilance Committee (CNPV) of 29/03/2011

Trimetazidine has been the subject of several pharmacovigilance updates and surveys since 2005; the results of the most recent survey were presented at the CNPV meeting on 29/03/2011.

The French National Pharmacovigilance Database (BNPV) was searched between 13 February 2008 and 3 January 2011. During this period, 86 cases [49 Serious (S), 36 Non Serious (NS) and 1 overdose without AE] from the BNPV were selected and analysed.

As regards the PSUR data sent by companies, over the period from 2008 to August 2010, 111 cases, including 68 duplicates with cases in the BNPV, were selected and analysed.

The adverse effects reported were the following:

- 28 cases of falls, arterial hypotension, faintness, dizziness, including 16 cases where the only suspect medicine is TMZ. Of the 14 cases of arterial hypotension or symptomatic orthostatic hypotension, 7 were serious cases involving falls.
- 63 cases of neurological effects, including 48 cases (45 of them in France) of Parkinsonian syndrome and other related motor disorders (tremor, muscular rigidity and gait disorders, restless legs syndrome) which nearly always occur in patients without any known previous Parkinsonism. In the majority of cases they are reversible on withdrawal of the TMZ, even months or years later;
- 15 cases of cardiac effects and other vascular effects;
- 21 cases of skin and mucosal manifestations;
- 5 cases of hepatic and pancreatic disorders;
- 9 cases of coagulation disturbances and bleeding;
- 9 cases of blood cell disorders.

Conclusions of the Pharmacovigilance rapporteur:

“The major problem with trimetazidine is, in particular, the neurological adverse effects. The diagnosis by practitioners of drug-induced Parkinsonism in the presence of trimetazidine is difficult to establish, despite its mention in the French SPC, on account of the age of the patients treated with trimetazidine and the possibility of the gradual aggravation of the symptoms, with a time to onset of several weeks or months. The risk of not evoking the role of trimetazidine is a worrying possibility in the case of disabling and chronic disorders, which

can regress just when discontinuation of the product is considered. What we have here therefore is a worrying problem of morbidity.

Moreover, unless a benefit from trimetazidine is demonstrated, the product's safety profile seems difficult to accept, given that it is a source of morbidity with a probably higher than usual level of under-reporting, because of the population involved (elderly/very elderly subjects) and the effects induced (Parkinsonian symptoms).

In the event that the MAs of trimetazidine-based proprietary medicinal products were to be maintained, the rapporteur suggests that they be put in List I, that patients undergo neurological examination before and during treatment with trimetazidine, and that they be contraindicated in Parkinson's patients."

3. MA Committee meeting of 07/04/2011

Following the pharmacovigilance survey relating to all of trimetazidine's adverse effects, conducted in 2008, the adverse effects section has been modified, new warnings have been added (Parkinsonism aggravated and induced and proneness to falling due either to arterial hypotension or postural instability), and trimetazidine has been put in List II of poisonous substances.

The pharmacovigilance survey conducted over the last three years (2007-2010) has resulted in over five hundred adverse effects being attributed to trimetazidine. Subjects aged at least 75 years account for only 14% of non-serious effects, but 25% of serious effects. Of the accepted adverse effects, we only quote the serious or new ones:

- arterial hypotension, dizziness, feeling faint and falling, which principally affect the elderly;
- an immuno-allergic potential, with numerous skin effects and, possible haematological effects,
- neurological effects, with Parkinsonian symptoms and related motor disorders predominating.

With reference to Parkinsonian symptoms, there were very few cases before 2005 recorded in the pharmacovigilance database and by pharmaceutical companies; in January 2011, there were 81 cases recorded and 10 cases since then. In the last three years, 45 patients were affected by Parkinsonism. Considering that only 5% of cases are notified, the 45 cases found in the last three years extrapolate to 900 cases. It should be emphasised that in the majority of cases trimetazidine is the only cause attributed to these symptoms. The youngest subject in whom the symptoms were found was aged 58 years. Exacerbation of pre-existing Parkinson's disease due to taking trimetazidine has been observed in only one case. It would seem, therefore, that trimetazidine induces or reveals Parkinsonism.

The median time to onset of symptoms is 400 days; but some have appeared in subjects after only some years of treatment.

In conclusion, unless a significant benefit of this drug is demonstrated for the patients, , trimetazidine's safety profile would seem to be unacceptable, given that it is the source of a worrying morbidity, induced in particular by Parkinsonian symptoms, and this especially so given its probable under-reporting.

5 TRANSPARENCY COMMITTEE CONCLUSIONS

5.1. Reassessment of the actual benefit

Stable angina

Stable chronic angina is most often a manifestation of ischaemic heart disease. It is a frequent, serious and potentially life-threatening condition.

In light of the mild effect size in the treatment of angina pectoris and the risk of serious adverse events being triggered by the use of trimetazidine [neurological manifestations (Parkinsonian symptoms and related motor disorders, dizziness, feeling faint and proneness to falls), immuno-allergic potential (skin conditions) and haematological disorders (thrombopenia)], a source of worrying morbidity, especially in elderly subjects, the efficacy/adverse effects ratio of these proprietary medicinal products in this indication is unfavourable when compared to that of the other available treatments.

There are numerous treatment alternatives.

Public health benefit:

Stable chronic angina is a frequent and serious disease situation. Its burden in terms of public health is considerable.

Improvement in the treatment of ischaemic heart disease is a public health need which is an established priority (French 2004 Law on Public Health*, GTNDO**).

In light of the results from the available clinical trials, the benefit of the proprietary medicinal product VASTAREL is not proven. The safety data reveal the onset of serious adverse events, symptoms of Parkinsonism in particular. Given the high number of patients treated in France, the question of a negative population effect does arise.

Overall, the public health benefit offered by VASTAREL is negative.

* Law No. 2004-806 of 9 August 2004 on public health policy. [rapport_DREES_indicateurs – July 2005]

** GTNDO: Groupe Technique National de Définition des Objectifs [National technical group for setting of public-health objectives] (DGS [Ministry of Health]-2003)

The actual benefit of VASTAREL (trimetazidine) and its generics is insufficient compared to that of other available treatments to justify its reimbursement by public funds, given the mild effect size and the risks of onset of serious adverse events (both neurological and haematological) associated with its use.

Vertigo and tinnitus

The syndromes of dizziness and/or tinnitus do not, as a general rule, entail either any serious complications or disability but can, on account of their persistent nature, involve a sometimes marked impairment in the quality of life.

These proprietary medicinal products are symptomatic treatments.

In light of the inadequately size effect in the treatment of dizziness and tinnitus and the risk of serious adverse events being triggered by the use of trimetazidine [neurological manifestations (Parkinsonian symptoms and related motor disorders, dizziness, feeling faint and proneness to falls), immuno-allergic potential (skin conditions) and haematological disorders (thrombopenia)], a source of worrying morbidity, especially in elderly subjects, the efficacy/adverse effects ratio of these proprietary medicinal products in this indication is unfavourable when compared to that of the other available treatments.

There are medicinal and non-medicinal treatment alternatives to these proprietary medicinal products.

Public health benefit:

The public health burden of dizziness and tinnitus is small. Improving their treatment does not constitute a public health need.

The available data do not allow any conclusion to be drawn as to VASTAREL's impact in terms of improving quality of life by comparison with the usual treatment strategy. In light of the tolerability data, which reveal the occurrence of serious adverse events, including Parkinsonian syndrome, and the large number of patients treated, the question of a negative population impact does arise.

Overall, the public health interest offered by VASTAREL is negative.

The actual benefit of VASTAREL (trimetazidine) and its generics is insufficient compared to that of other available treatments to justify its reimbursement by public funds, given the poorly established effect and the risks of onset of serious adverse events (both neurological and haematological) associated with its use.

5.2. Transparency Committee recommendations

The transparency Committee is not in favour of the continued inclusion of VASTAREL and its generics on the list of medicines reimbursed by National Health Insurance and on the list of medicines approved for hospital use and various public services in the indication and at the dosage in the Marketing Authorisation.

The Transparency Committee recommends removal from the list of medicines reimbursed by National Health Insurance and from the list of medicines approved for hospital use and various public services.

Appendix

1. Bruce protocol (1971)

Stage	Minutes	Speed in km/h	Slope in degrees	Slope in %
I	3	2.7	5.7	10
II	3	4.0	6.9	12
III	3	5.5	8.0	14
IV	3	6.8	9.1	16
V	3	8.0	10.3	18

2. Emeriau study⁹

The initial objective of the randomised, double-blind Emeriau study was to assess the primary safety and the interpretation of the serious adverse effects as a function of the pharmacokinetics of VASTAREL 70 mg/day in two intakes in elderly and very elderly patients followed up for 12 months.

Results:

- the number of falls was greater in the group of patients treated with trimetazidine,
- the number of serious adverse effects is larger when the area under the concentration curve is three times greater than a reference area under the curve.
- significant concentrations of trimetazidine have been observed in some very elderly subjects, which raises a question mark over the safety of this medicinal product in these patients.
- the peak plasma trimetazidine concentration, which is less than 100 ng/ml in young healthy subjects who have received 20 mg trimetazidine, can be several times higher in elderly and/or renal failure subjects.

⁹ MA Committee of 07/04/2011