CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Ramipril Aurobindo 1.25 mg, 2.5 mg, 5 mg and 10 mg, capsules, hard Aurobindo Pharma B.V., the Netherlands

ramipril

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB.
It reflects the scientific conclusion reached by the MEB at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

Registration number in the Netherlands: RVG 105268, 105271, 105272, 105274

19 December 2012

Pharmacotherapeutic group:	ACE inhibitors, plain
ATC code:	C09AA05
Route of administration:	oral
Therapeutic indication:	hypertension; cardiovascular prevention; renal disease; symptomatic hear failure; secondary prevention after acute myocardial infarction.
Prescription status:	prescription only
Date of authorisation in NL:	23 August 2010
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board of the Netherlands (MEB) has granted a marketing authorisation for Ramipril Aurobindo 1.25 mg, 2.5 mg, 5 mg and 10 mg, capsules, hard from Aurobindo Pharma B.V. The date of authorisation was on 23 August 2010 in the Netherlands.

The product is indicated for:

- Treatment of hypertension.
- Cardiovascular prevention: reduction of cardiovascular morbidity and mortality in patients with
  - manifest atherothrombotic cardiovascular disease (history of coronary heart disease or stroke, or peripheral vascular disease) or
  - diabetes with at least one cardiovascular risk factor (see section 5.1).
- Treatment of renal disease:
  - incipient glomerular diabetic nephropathy as defined by the presence of microalbuminuria,
  - manifest glomerular diabetic nephropathy as defined by macroproteinuria in patients with at least one cardiovascular risk factor (see section 5.1),
  - manifest glomerular non diabetic nephropathy as defined by macroproteinuria ≥ 3 g/day (see section 5.1).
- Treatment of symptomatic heart failure.
- Secondary prevention after acute myocardial infarction: reduction of mortality from the acute phase of myocardial infarction in patients with clinical signs of heart failure when started > 48 hours following acute myocardial infarction.

A comprehensive description of the indications and posology is given in the SPC.

Ramiprilat, the active metabolite of the prodrug ramipril, inhibits the enzyme dipeptidylcarboxypeptidase I (synonyms: angiotensin-converting enzyme; kininase II). In plasma and tissue this enzyme catalyses the conversion of angiotensin I to the active vasoconstrictor substance angiotensin II, as well as the breakdown of the active vasodilator bradykinin. Reduced angiotensin II formation and inhibition of bradykinin breakdown lead to vasodilatation.
Since angiotensin II also stimulates the release of aldosterone, ramiprilat causes a reduction in aldosterone secretion. The average response to ACE inhibitor monotherapy was lower in black (Afro-Caribbean) hypertensive patients (usually a low-renin hypertensive population) than in non-black patients.

This national procedure concerns a generic application claiming essential similarity with the innovator product Tritace 1.25, 2.5, 5 and 10, capsules (NL License RVG 13294-13297), which have been registered by Sanofi-Aventis Netherlands B.V since 16 May 1990.

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Tritace® Capsules 10 mg, registered in the Netherlands. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is ramipril, an established active substance described in the European Pharmacopoeia (Ph.Eur.*) It is sparingly soluble in water and freely soluble in methanol. No polymorphs of ramipril have been reported in the literature. However, a single crystalline form is produced.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is in accordance with the CEP. Batch analytical data have been submitted, demonstrating compliance with the drug substance specification.

Stability of drug substance
Stability data on the active substance have been provided for three batches stored at 25°C/60% RH for 48 months and 40°C/75% RH for 6 months. Photostability studies have been performed and it was shown that ramipril active substance is photostable. Given the observed trends, a re-test period of 2 years when preserve in well closed containers at controlled temperature (15°C to 30°C).

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Ramipril Aurobindo 1.25 mg is a yellow/white size ‘4’ hard gelatin capsule imprinted with ‘D’ on yellow cap and ‘40’ on white body with black edible ink filled with white to almost white powder
Ramipril Aurobino 2.5 mg is an orange/white size ‘4’ hard gelatin capsule imprinted with ‘D’ on orange cap and ‘41’ on white body with black edible ink filled white to almost white powder.
Ramipril Aurobino 5 mg is a red/white size ‘4’ hard gelatin capsule imprinted with ‘D’ on red cap and ‘42’ on white body with black edible ink filled with white to almost white powder.
Ramipril Aurobino 10 mg is a blue/white size ‘4’ hard gelatin capsule imprinted with ‘D’ on blue cap and ‘43’ on white body with black edible ink filled with white to almost white powder.

The hard capsules are packed in PVC/PA/PVC-Al blister packs or white HDPE bottles with PP closure.

The excipients are: pregelatinized starch and colloidal anhydrous silica. The capsules contain:
1.25 mg – gelatin, sodium lauryl sulphate, iron oxide yellow (E172), titanium dioxide (E171)
2.5 mg – gelatin, sodium lauryl sulphate, iron oxide yellow (E172), Ponceau 4R (E124), titanium dioxide (E171)
5 mg and 10 mg – gelatin, sodium lauryl sulphate, Ponceau 4R (E124), Patent Blue V (E131), titanium dioxide (E171).

The capsules are non-dose weight proportional. The difference due to content of active component in various strengths is compensated by the excipient pregelatinized starch. The different strengths are weight similar.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The formulation was initiated based on characterisation of the innovator product and active substance and compatibility testing with excipients. The aim was to develop look-alike formulations for the different strengths by keeping the average weight the same with different coloured capsules.
Tritace 10mg capsules from Aventis Pharma B.V. in the Netherlands was compared against Ramipril Aurobindo 10 mg capsules in the bioequivalence study. The test and reference drug compare well with respect to impurity profiles and assay content. Comparative dissolution studies with the batches used in the bioequivalence study show that both test and reference products dissolve very rapidly, *i.e* ≥ 85% in 15 min, and may therefore be considered to have similar dissolution profiles. Ramipril 1.25 mg, 2.5 mg and 5 mg were then compared against the 10 mg strength of Ramipril, All four strengths dissolve very rapidly, *i.e.* ≥ 90% in 15 min and the dissolution profiles are thus regarded as similar. The pharmaceutical development has been sufficiently elucidated.

Manufacturing process
The manufacturing process is straightforward. Because of the active substance's sensitivity to moisture the starch is pre-dried. Ramipril and the excipients are sifted, blended and filled into hard gelatin capsules. Process validation data on the product has been presented for two pilot-scale batches of each of the four strengths. The product is manufactured using conventional manufacturing techniques. However, since the two lower strengths contain the active substance at a low concentration (≤ 2%), the process is regarded as a non-standard process. Validation data of the maximum proposed commercial batch size does not have to be submitted pre-registration as the process at the minimum scale is considered to be representative for the maximum scale with respect to homogeneity of the substance.

Control of excipients
The excipients comply with the Ph.Eur. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, identification (active substance and colourants), average fill weight, dissolution, content uniformity, assay, related substances, loss on drying and microbial contamination. The release and shelf-life specifications are acceptable. The analytical methods have been adequately described and validated.
Batch analytical results from the proposed production site have been provided on two batches of each of the four strengths on pilot scale, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for two batches of each strength stored at 25°C/60% RH (18 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). The batches were stored in blister packaging, HDPE containers with PP closures and silica sachets, and simulated bulk packaging. Significant changes were observed in assay values, dissolution and one impurity at accelerated conditions in both the blister packs and HDPE containers. At intermediate conditions the impurity increases also during storage, but this is less pronounced than observed in the accelerated studies. At long term conditions the impurity increases gradually over time, but still remains within the limit and no significant

changes are noted in any of the other parameters. Extrapolation of the data is only partly acceptable and therefore a shelf life of 21 months when stored below 25°C was granted. Photostability of the product has been demonstrated. The drug product should be stored in the original packaging in order to protect from moisture. The shelf life has been extended to 24 months through a type IB variation (see page 11).

In-use stability
In-use studies were done for the 1.25 mg and 10 mg strength and the lowest count, i.e. 30 capsules, and the largest count, i.e. 1000 capsules of the container packs were chosen. An in-use period of 90 days was granted based on the available in-use stability data. This period applies to the 30's and 100's count containers; the 500's and 1000's count containers are for hospital/pharmacy use.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
As certified by the respective suppliers of silica and starch, no materials of plant or animal origin are used during the manufacture of these materials, nor do they come in contact with the plant or animal products during storage and shipment. Thus, there is no risk of BSE/TSE with the said material.
For the capsule shells, the gelatin used in the manufacturing is procured from a manufacturer who has been issued a valid certificate of suitability by the EDQM; hence the gelatin does not possess any risk of TSE. All the raw materials used in the manufacturing of the printing ink are of synthetic origin, except for Shellac which is derived from LAC Insect. As per the justification of the ink manufacturer, shellac is unlikely to pose any risk of TSE/BSE.

II.2 Non clinical aspects

This product is a generic formulation of Tritace, which is available on the European market. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the Board agreed that no further non-clinical studies are required.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of ramipril released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Ramipril is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the Board agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Ramipril Aurobino 10 mg (Aurobindo Pharma B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Tritace® capsules 10 mg (Aventis Pharma BV, the Netherlands).

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 42 healthy male subjects, aged 18-42 years. Each subject received a single dose (10 mg) of one of the 2 ramipril formulations. The tablet was orally administered

with 240 ml water after an overnight fast of 10 hours. There were 2 dosing periods, separated by a washout period of 22 days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.50, 0.67, 0.83, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 48, 72, 120, 168, 216 and 288 hours after administration of the products.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
Only the samples of the 41 volunteers who completed the study were analysed. One subject dropped out the study as he was absent for period-II check in.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of ramipril under fasted conditions.

Treatment N=41	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	35 ± 26	36 ± 26	51 ± 35	0.50 (0.33-1.25)	1.14 (± 0.67)
Reference	39 ± 33	39 ± 34	55 ± 51	0.50 (0.33-1.00)	1.47 (± 0.92)
***Ratio (90% CI)**	0.97 (0.88-1.08)	0.97 (0.88-1.07)	1.03 (0.91-1.17)	-	-
CV (%)	28	27	34	-	-

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of ramiprilat under fasted conditions.

Treatment N=41	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	390 ± 188	526 ± 299	28 ± 23	2.50 (1.25-6.00)	193 (±174)
Reference	398 ± 189	507 ± 239	29 ± 17	2.00 (1.25-5.00)	165(±69)
***Ratio (90% CI)**	0.99 (0.93-1.03)	1.00 (0.94-1.06)	0.94 (0.86-1.02)	-	-
CV (%)	-	-	-	-	-

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of ramipril, supported by those of the active metabolite ramiprilat under fasted conditions, it can be concluded that Ramipril Aurobino 10 mg and Tritace® 10 mg capsules are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Ramipril may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of ramipril. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Biowaiver
A biowaiver for the 1.25, 2.5 and 5 mg capsules, based on the following criteria:

- Ramipril 1.25 mg, 2.5 mg, 5 mg & 10 mg capsules are manufactured by the same manufacturer using the same manufacturing process.
- Ramipril demonstrates linear pharmacokinetics over the therapeutic dosage range.
- The qualitative composition of Ramipril 1.25 mg, 2.5 mg & 5 mg capsules is the same as that of Ramipril 10 mg capsules.
- Ramipril 1.25 mg, 2.5 mg and 5 mg capsules are weight similar to Ramipril 10 mg capsule. The ratio between amounts of excipients is similar, but not the same for all strengths. The content of active substance in the 1.25 mg, 2.5 mg and 5 mg strengths is less than 5%, whereas the content of active substance in the 10 mg strength is about 8%. The formulation contains only two excipients: pre-gelatinized starch and silica hydrophobic colloidal anhydrous. The difference due to content of active component in various strengths is compensated by excipient pregelatinized starch. The MAH states that the different strengths of Ramipril capsules can be considered as proportional (*i.e.* weight similar), taking into consideration that the bioequivalence study is conducted on the highest dose using the highest strength (*i.e.* 10 mg).
- The dissolution profile of Ramipril 1.25 mg, 2.5 mg and 5 mg capsules is similar to Ramipril 10 mg capsules. All four strengths dissolve very rapidly, *i.e.* ≥ 90% in 15 min.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Risk management plan
Ramipril was first approved in 1989, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of ramipril can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC
The content of the SPC approved during the decentralised procedure is in accordance with that for the innovator product.

Readability test
The package leaflet has not been evaluated via a user consultation study. Instead, a bridging statement was submitted. The PIL for Ramipril Aurobindo 1.25 mg, 2.5 mg, 5 mg & 10 mg capsules, hard (Daughter PIL) contains the same text of Ramipril Aurobindo 5 mg & 10 mg tablets (Parent PIL). Since both parent

and daughter PIL contains same active ingredient all the important key messages for safe use are same in both Patient Information Leaflets. The differences are minor and particular to the pharmaceutical form, excipients and pack sizes. The layout and design are similar.
Furthermore, the PIL text is in line with the harmonised product information of the reference product Tritace, for which an article 30 harmonisation procedure was finalised (6 March 2009). No separate user testing is required.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Ramipril Aurobindo 1.25 mg, 2.5 mg, 5 mg and 10 mg, capsules, hard have a proven chemical-pharmaceutical quality and are generic forms of Tritace 1.25, 2.5, 5 and 10 mg, capsules. Tritace is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors. The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated with the reference product, and has therefore granted a marketing authorisation. Ramipril Aurobindo 1.25 mg, 2.5 mg, 5 mg and 10 mg, capsules, hard were authorised in the Netherlands on 23 August 2010.

There were no post-approval commitments made during the procedure.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Transfer of the marketing authorisation.	--	MA transfer	21-10-2010	16-11-2010	Approval	N
Change in the name of the medicinal product.	--	IA	25-7-2011	5-8-2011	Approval	N
Extension of shelf life of the finished product from 21 months to 24 months based on available long term stability data.	--	IB	17-10-2011	8-11-2011	Approval	N