CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Perindopril tert-butylamine Aurobindo 2 mg, 4 mg and 8 mg, tablets Aurobindo Pharma B.V., the Netherlands

perindopril tert-butylamine

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 and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states 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.

EU-procedure number: NL/H/2291/001-003/MR
Registration number in the Netherlands: RVG 105834-105836

31 October 2011

Pharmacotherapeutic group:	ACE inhibitors, plain
ATC code:	C09AA04
Route of administration:	oral
Therapeutic indication:	hypertension; stable coronary artery disease; symptomatic heart failure (2 and 4 mg)
Prescription status:	prescription only
Date of first authorisation in NL:	9 August 2010
Concerned Member States:	Mutual recognition procedure with ES, FR, MT, PL, UK
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 member states have granted a marketing authorisation for Perindopril tert-butylamine Aurobindo 2 mg, 4 mg and 8 mg, tablets from Aurobindo Pharma B.V. The date of authorisation was on 9 August 2010 in the Netherlands.

The product is indicated for:
- treatment of hypertension
- treatment of symptomatic heart failure (2 and 4 mg only)
- treatment of stable coronary artery disease; reduction of the risk of cardiac events in patients who have a history of myocardial infarction and/or revascularisation.

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

Perindopril inhibits the enzyme which converts angiotensin I into angiotensin II (angiotensin-converting enzyme (ACE)). The converting enzyme or kinase is an exopeptidase which converts angiotensin I into the vasoconstrictor angiotensin II and degrades the vasodilator bradykinin in to an inactive heptapeptide. Inhibition of the ACE results in a reduction in the plasma levels of angiotensin II, which leads to an increase in renin activity in the plasma (as a result of the inhibition of the negative feedback from the renin release) and a reduction in the secretion of aldosterone. As ACE inactivates bradykinin, the inhibition of ACE also results in the increased activity of the circulating and local kallikrein-kinin systems (and consequently also the activation of the prostaglandin system). It is possible that this mechanism contributes to the antihypertensive activity of the ACE inhibitors and is partly responsible for some of their side effects (e.g. cough).
Perindopril acts via its active metabolite, perindoprilat. The other metabolites do not show any inhibition of ACE activity *in vitro*.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Coversyl 2 mg, 4 mg and 8 mg tablets which have been registered in France by Les Laboratoires Servier since 22 June 1988. In the Netherlands, Coversyl 2 mg and 4 mg tablets have been registered since 17 July 1989, and Coversyl 8 mg tablets since 14 April 2003 (NL RVG 13635, 13636 and 27786 respectively). In addition, reference is made to Coversyl authorisations in the individual member states (reference product).

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 8 mg product is compared with the pharmacokinetic profile of the reference product Coversyl 8 mg tablets, registered in UK. 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 perindopril tert-butylamine, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is freely soluble in water and in ethanol (90%), soluble or sparingly soluble in methylene chloride. Perindopril tert-butylamine exists in various polymorphic forms. Only the (α)-form is manufactured.

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 new 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 line with the Ph.Eur. and the CEP, with some additional in-house parameters. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analyses data on three production scale batches has been provided. All three batches meet the proposed set of specifications.

Stability of drug substance
The active substance is stable for 24 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

**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
Perindopril tert-butylamine Aurobindo 2 mg is a white to off-white coloured, round biconvex, uncoated tablet with debossing “D” on one side and “57”on the other side.
Perindopril tert-butylamine Aurobindo 4 mg is a white to off-white coloured, capsule shaped, uncoated tablet with debossing “D” on one side and “5” & “8” on either side of the break line on another side. The tablet can be divided into two equal halves.
Perindopril tert-butylamine Aurobindo 8 mg is a white to off-white coloured, round biconvex, uncoated tablet with debossing “D” on one side and “5” & “9” on either side of the break line on another side. The tablet can be divided into two equal halves.

The tablets are packed in PVC/PVDC/Aluminium blisters are packed in a foil pouch containing a desiccant.

The excipients are: lactose anhydrous, colloidal anhydrous silica (E 551), microcrystalline cellulose (E 460), magnesium stearate (E 572).

All three tablet strengths are fully dose proportional.

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. Development was started with the 8 mg strength, and a direct compression method. During the development the composition and process parameters were optimised several times until the final composition and manufacturing method was obtained. Then the product was scaled down to the 2 and 4 mg strength.

The composition of the batch used in the bioequivalence study is identical to the proposed composition and the optimised manufacturing process as described in the dossier was used. Dissolution data of the batches used in the bioequivalence study show that in all 3 media used the tablets dissolve very rapidly (>85% in 10 minutes), so the dissolution characteristics of the test and reference product are similar throughout the physiological pH range. As reference product in the bioequivalence and the dissolution study, the UK reference product was used. The dissolution profile of the current drug product and the Dutch and UK reference products have been compared. In all 3 media used, all three tablets show rapid dissolution (> 85% dissolved in 15 minutes). The use of the UK reference product in the bioequivalence study is acceptable.

The 4 and 8 mg tablets bear a breakline, and therefore the subdivision of the tables was tested according to the current Ph.Eur. criteria. The tablets comply with the Ph.Eur. criteria.

The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process consists of mixing, blending and compression, which is considered a standard process. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for 2 production-scale batches of each tablet strength. The product is manufactured using conventional manufacturing techniques. Process validation for full-scaled batches will be performed post authorisation.

Control of excipients

The excipients comply with Ph.Eur. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance, identity, thickness, average weight, assay, related substances, water, uniformity of dosage units and microbial contamination.

With the exception of the specification for the assay and the degradation products, the release and end of shelf-life specifications are identical. The proposed release and end of shelf-life limits are acceptable. As degradation mainly occurs after opening of the pouch, separate end-of-shelf-life specifications are applied to the limits for related substances in the unopened and opened drug product.

The analytical methods have been adequately described and validated.

Batch analytical data from the proposed production site have been provided for 2 batches of each strength, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided for 2 batches commercial-scale batches of each strength stored at 25°C/60%RH (36 months) and 40°C/75%RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in clear PVC/PVdC – Al foil blisters packed in triple laminated pouch. On the basis of the submitted stability data a shelf life of 24 months can be granted, when stored below 25°C. The product is susceptible to light and moisture so should be stored in the original container.

Stability data has been provided demonstrating that the product remains within limits for 90 days following opening of the laminated pouch, when stored below 25°C. However, an in-use shelf-life of 60 days is applied. This is acceptable.

Several post-approval commitments have been made with regard to the finished product; these can be found on page 8 of this report.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose is obtained from milk from healthy cows in the same conditions as milk collected for human consumption. Also, the calf rennet used in manufacture of lactose is produced in accordance with the applicable EU requirements. Hence, there is no likelihood of any TSE-risk associated with lactose. Magnesium stearate is produced with tallow derived stearic acid in agreement with the current CPMP guidelines towards minimizing risk of BSE transmission.

II.2 Non-clinical aspects

These products are generic formulations of Coversyl 2 mg, 4 mg and 8 mg tablets, which are available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

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 perindopril tert-butylamine 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

Perindopril tert-butylamine is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Perindopril tert-butylamine Aurobindo 8 mg (Aurobindo Pharma B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Coversyl 8 mg tablets (Servier Laboratories, France) from the UK market.

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design
An open label, single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 28 healthy male subjects, aged 18-42 years. Each subject received a single dose (8 mg) of one of the 2 perindopril formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were 2 dosing periods, separated by a washout period of 15 days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.5, 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, 36, 48 and 72 hours after administration of the products.

Analytical/statistical methods
Plasma samples were analysed for perindopril and its active metabolite, perindoprilat. 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

Two subjects dropped out from the study as they were absent for period 2. One subject was withdrawn from the study due to an adverse event after the 36 hour sample time point in period 2. The remaining 25 subjects completed the study and were included in the pharmacokinetic analysis.

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

Treatment N=25	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	112.4 ± 34.1	113.4 ± 34.3	94.0 ± 33.1	0.67 (0.33 – 1.75)	0.79 ± 0.12
Reference	106.2 ± 30.4	107.4 ± 30.6	86.3 ± 30.0	0.67 (0.50 – 1.25)	0.80 ± 0.12
***Ratio (90% CI)**	1.05 (0.99 – 1.12)	1.05 (0.99 – 1.11)	1.10 (0.99 – 1.23)	--	--
CV (%)	12.2	11.9	23.2	--	--

$AUC_{0-\infty}$ 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 perindoprilat under fasted conditions.

Treatment N=25	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	124.6 ± 32.6	156.6 ± 44.7	6.97 ± 2.38	5.0 (3.5 – 8.0)	35.9 ± 16.9
Reference	122.4 ± 34.8	159.3 ± 52.6	6.71 ± 2.74	5.0 (3.5 – 10)	41.5 ± 20.1
***Ratio (90% CI)**	1.01 (0.98 – 1.06)	0.99 (0.92 – 1.06	1.04 (0.98 – 1.11)	--	--
CV (%)	8.1	14.0	13.4	--	--

$AUC_{0-\infty}$ 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 perindopril supported by the data of perindoprilat under fasted conditions, it can be concluded that Perindopril tert-butylamine Aurobindo 8 mg and Coversyl 8 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

It is known that ingestion of food decreases conversion to perindoprilat, hence bioavailability. It is stated in the SPC that perindopril should be administered orally in a single daily dose in the morning before a meal. Therefore the bioequivalence study only under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Extrapolation to different strengths
According to the CPMP guideline "Note for guidance on the investigation of bioavailability and bioequivalence" (CPMP/EWP/QWP/1401/98), a bioequivalence study investigating only one tablet strength may be acceptable if all of the following conditions are fulfilled:

- the pharmaceutical products are manufactured by the same manufacturer and process
- the pharmacokinetics has been shown to be linear over the therapeutic range
- the qualitative composition of the different strengths is the same
- the ratio between amounts of active substance and excipients is the same
- the dissolution profile should be similar under identical conditions for the additional strengths and the strength of the biobatch

All these conditions hold for Perindopril tert-butylamine Aurobindo. Therefore it can be considered that the 2 and 4 mg tablet formulations would also be bioequivalent to their respective Coversyl® counterparts. Dissolution profiles at three pH's were submitted comparing all three strengths.

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
Perindopril tert-butylamine was first approved in 1988, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of perindopril tert-butylamine 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 mutual recognition procedure is in accordance with that accepted for the reference product Coversyl.

Readability test
The package leaflet has not been evaluated via a user consultation study. Reference is made to a user test on the PIL for another ACE inhibitor. The bridging report states that the key messages for safe use are the same in both PILs and were investigated during the user test. Furthermore, the design and layout of the PILs are similar and both are formatted in line with the QRD template. The user testing results demonstrated that the layout of the PIL and the general readability were satisfactory, so the leaflet is considered acceptable. The bridging report is therefore accepted and no separate user testing is required.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Perindopril tert-butylamine Aurobindo 2 mg, 4 mg and 8 mg, tablets have a proven chemical-pharmaceutical quality and are generic forms of Coversyl 2 mg, 4 mg and 8 mg tablets. Coversyl 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, package leaflet and labelling are in the agreed templates and are in agreement with other perindopril tert-butylamine containing products.

The Board followed the advice of the assessors. Perindopril tert-butylamine Aurobindo 2 mg, 4 mg and 8 mg, tablets were authorised in the Netherlands on 9 August 2010.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Perindopril tert-butylamine Aurobindo 2 mg, 4 mg and 8 mg, tablets with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 17 July 2011.

The date for the first renewal will be: 30 April 2014.

The following post-approval commitments have been made during the procedure:

<u>Quality - medicinal product</u>

- The MAH committed to include the first three batches of each strength with the maximum batch size and first commercial batch of 2mg strength in the stability program.
- The MAH committed to include at least one marketed production batch per year in the stability program.
- The MAH committed to perform the stability studies for the commercial batches at an intermediate condition if a significant change occurs during the accelerated stability study.

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