CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Perindopril tert-butylamine Glenmark 2 mg, tablets
Perindopril tert-butylamine Glenmark 4 mg, tablets
Perindopril tert-butylamine Glenmark 8 mg, tablets
Glenmark Pharmaceuticals Europe Ltd, United Kingdom

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/1336/001-003/MR
Registration number in the Netherlands: RVG 101725, 101755, 101757

10 March 2010

Pharmacotherapeutic group:	ACE inhibitors, plain
ATC code:	C09AA04
Route of administration:	oral
Therapeutic indication:	hypertension; symptomatic heart failure; stable coronary artery disease
Prescription status:	prescription only
Date of first authorisation in NL:	26 March 2008
Concerned Member States:	Mutual recognition procedure with BG, CZ, EE, HU, LT, LV, PL, PT, RO, SI and SK
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)and 10(3)

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 Glenmark 2 mg, 4 mg and 8 mg, tablets from Glenmark Pharmaceuticals Europe Ltd. The date of authorisation was on 26 March 2008 in the Netherlands.

The product is indicated for:
- treatment of hypertension
- treatment of symptomatic heart failure
- 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. In some member states the marketing authorisation for the 2 mg tablet is granted according to Article 10(3) of Directive 2001/83/EC, hybrid application, as the 2 mg product is not authorised in these member states. The reference product is the 4 mg strength.

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 two bioequivalence studies in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product. For one study the reference product was Coversyl 4 mg tablets from the UK market, and for the other study Coversyl 8 mg tablets from the French market. 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. These generic products can be used instead of their reference products.

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 these product types 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.

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 suitablity 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.

Quality control of drug substance
The chemical-pharmaceutical documentation on the active substance is of sufficient quality in view of the present European regulatory requirements. The specification is in line with the Ph.Eur monograph. The additional CEP requirements and the in-house test have been included by the MAH. Batch analytical data demonstrating compliance with the drug substance specification have been provided for 3 production-scale batches. The MAH committed to, and has now submitted validation data for microbial contamination of the active substance.

Stability of drug substance
Stability data on the active substance have been provided for 3 batches in accordance with applicable European guidelines, demonstrating the stability of the active substance for 24 months. The substance was adequately stored. Based on the data submitted, a retest period could be granted of 24 months. No special storage condition is required.

** 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 Glenmark 2 mg contains as active substance 2 mg of perindopril tert-butylamine salt, corresponding to 1.669 mg perindopril, and is a white, round, biconvex tablet, smooth on both sides.

Perindopril tert-butylamine Glenmark 4 mg contains as active substance 4 mg of perindopril tert-butylamine salt, corresponding to 3.338 mg perindopril, and is a white, oblong tablet, with a break-line on both sides, ‘P P’ engraved on one side and ‘4’ on the other. The tablet can be divided into equal halves.

Perindopril tert-butylamine Glenmark 8 mg contains as active substance 8 mg of perindopril tert-butylamine salt, corresponding to 6.676 mg perindopril, and is a white, circular, biconvex tablet with ‘P P’ debossed on one side and ‘8’ on the other.

The tablets are packed in Aluminium/Aluminium blister packs.

The excipients are: hydrophobic colloidal silica, microcrystalline cellulose, lactose monohydrate, magnesium stearate.

The different strengths are fully dose proportional.

Pharmaceutical development
The development of the product has been described, the choice of excipients is adequately justified and their functions explained. The excipients and packaging are usual for this type of dosage form. The same excipients are used as in the brand formula.
Comparative dissolution profiles have been provided, using innovator tablets from Poland (4 mg), Denmark (2 mg, 4 mg, 8 mg), France (2 mg, 4 mg), Portugal (4 mg), Switzerland (4 mg), the Netherlands (2 mg, 4 mg, 8 mg) and UK (2 mg, 4 mg, 8 mg) versus the proposed product. The dissolution profiles are similar between innovator and proposed product.
The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process consists of blending the ingredients and direct compression. The manufacturing process has been sufficiently discussed. The process is considered a standard manufacturing process. Adequate validation data on three batches of the common blend and three production-scale batches of each tablet strength have been provided. The process is sufficiently under control.

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

Quality control of drug product
The finished product specifications are in line with the requirements of the current Ph.Eur. and ICH guidelines. The specification includes tests for appearance, identification, avarage weight, dimensions, resistance to crushing, friability, disintegration time, dissolution, uniformity of dosage units, related substances, assay, water content and microbial limits. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on 3 production-scale batches of each strength, demonstrating compliance with the specification. The MAH commited to validate the first three commercial batches of product of each strength as per the approved process validation protocol as enclosed in the dossier, following launch in the first instance and following scale-up, as applicable, for the larger batch sizes.
Also, the MAH committed that shipping will be in controlled conditions to ensure the product is maintained at the recommended storage conditions. Data loggers will be used with all shipments.

Stability tests on the finished product
The stability of the product has been investigated under ICH long term, intermediate and accelerated conditions. The product is unstable at accelerated conditions. Also some out-of-specification results were observed at intermediate conditions. The storage conditions have therefore been set at *'Do not store above 30°C'* and *'store in the original package in order to protect from humidity'.* On basis of the data submitted, a shelf life was granted of 2 years. The MAH committed to place the first three commercial batches of all strengths on stability in accordance with the approved protocol.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
The magnesium stearate used is of vegetable origin. Lactose is of animal origin, but a statement is enclosed regarding compliance for TSE.

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 two bioequivalence studies. In one study the pharmacokinetic profile of the test product Perindopril tert-butylamine Glenmark 4 mg (Glenmark Pharmaceuticals Europe Ltd) is compared with the pharmacokinetic profile of the reference product Coversyl 4 mg tablets ((Servier Laboratories, France) from the UK market.
The other study was performed with the 8 mg tablet and the reference product Coversyl 8 mg tablets (Servier Laboratories, France).

The choice of the reference product
The choice of the reference products 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.

Bioequivalence study with 4 mg

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 36 healthy male subjects, aged 19-33 years. Each subject received a single dose (4 mg) of one of the 2 perindopril formulations. The tablet was orally administered with 240 ml water. There were 2 dosing periods, separated by a washout period of at least 28 days.

Blood samples were collected pre-dose and at 0.16, 0.33, 0.5 0.75, 1.0. 1.25, 1.5 1.75, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 18.0, 24.0, 48.0, 72.0, 96.0 and 120.0 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
One subject was withdrawn due to a viral fever prior dosing in period I. The remaining 35 subjects completed the study. One of these subjects was excluded for the pharmacokinetic and statistical analysis of perindoprilat because the pre-dose concentration of period II was greater than 5 % of the respective C_{max} in that period. Plasma samples of 35 subjects were analysed for perindopril, and of 34 subjects for perindoprilat.

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

Treatment N=35	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	65.8 ± 13.8	70.0 ± 14.3	56.6 ± 12.2	0.50 (0.33 - 1.75)	0.82 ± 0.17
Reference	69.6 ± 14.2	73.4 ± 14.4	56.6 ± 13.5	0.75 (0.50 - 2.00)	0.80 ± 0.13
***Ratio (90% CI)**	0.94 (0.91-0.98)	0.95 (0.92-0.99)	1.00 (0.94-1.07)	-	-
CV (%)	9.8	9.7	16	-	-

$AUC_{0-\infty}$ 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=34	**AUC_{0-120h}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	261 ± 57	441 ± 177	6.2 ± 2.5	8.0 (4.0 - 12.0)	103 ± 64
Reference	249 ± 63	389 ± 104	6.0 ± 2.4	8.0 (4.0 - 12.0)	85 ± 42
***Ratio (90% CI)**	1.07 (1.00-1.14)	1.07 (0.97-1.18)	1.02 (0.95-1.10)	-	-
CV (%)	17	24	19	-	-

$AUC_{0-\infty}$ 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.
The terminal elimination half-life of perindoprilat observed during the study for the reference product was 103 hours and for the test product it was 85 hours. This difference in the half-life could be attributed to the variable nature of perindoprilat dissociation from the binding sites. Additionally, it can be remarked that as sampling was stopped at 120 hours, a precise elimination half-life is therefore difficult to establish. The extrapolation of the AUC of perindoprilat was more than 20% caused by the long half-life of perindoprilat. Based on the pharmacokinetic parameters of perindopril supported by the data of perindoprilat under fasted conditions, it can be concluded that Perindopril tert-butylamine Glenmark 4 mg and Coversyl 4 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.

Bioequivalence study with 8 mg

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 36 healthy male subjects, aged 18-36 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. There were 2 dosing periods, separated by a washout period of at least 42 days.

Blood samples were collected pre-dose and at 0.16, 0.33, 0.5 0.75, 1.0. 1.25, 1.5 1.75, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 18.0, 24.0, 48.0, 72.0, 96.0 and 120.0 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
Of the 36 subjects 30 subjects completed all study periods. A total of 5 subjects did not show up for the second period and one was withdrawn on medical grounds (fever). Two more subjects were excluded from statistical analysis of perindoprilat because they did not show up for the 48, 72, 96 hours ambulatory blood samples (one subject did also not show up for the 120 hours sample).
Plasma samples of 30 subjects were analysed for perindopril, and of 28 subjects for perindoprilat. In this study the $AUC_{0\text{-}inf}$ for perindoprilat was not reported. This is acceptable because the terminal half-life of perindoprilat is difficult to establish as the half life is often reported to be up to 120 hours and after 120 hours sampling absorption can be considered complete. Therefore, the $AUC_{0\text{-}120h}$ is in this case an acceptable parameter to establish bioequivalence.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of perindopril under fasted conditions.

Treatment N=30	**$AUC_{0\text{-}t}$** ng.h/ml	**$AUC_{0\text{-}\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	140 ± 27	144 ± 28	129 ± 26	0.50 (0.33 - 1.50)	0.77 ± 0.11
Reference	139 ± 27	142 ± 27	123 ± 29	0.50 (0.33 - 1.75)	0.77 ± 0.10
***Ratio (90% CI)**	1.01 (0.91-0.98)	1.01 (0.97-1.06)	1.05 (0.95-1.16)	-	-
CV (%)	10.8	10.4	22.6	-	-
$AUC_{0\text{-}\infty}$ area under the plasma concentration-time curve from time zero to infinity **$AUC_{0\text{-}t}$** 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 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of perindoprilat under fasted conditions.

Treatment N=28	**$AUC_{0\text{-}120h}$** ng.h/ml	**$AUC_{0\text{-}\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	221 ± 67	-	12.5 ± 4.0	5.0 (2.5 - 10.0)	-

Reference	226 ± 68	-	13.0 ± 4.5	5.0 (3.0 - 8.0)	-
***Ratio (90% CI)**	0.98 (0.93-1.02)	-	0.97 (0.92-1.03)	-	-
CV (%)	10.3	-	12.9	-	-

$AUC_{0-\infty}$ 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 calculated confidence intervals for AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} of perindopril and AUC_{0-120h} and C_{max} of perindoprilat are within the 0.80 – 1.25. acceptance range for bioequivalence. Based on the pharmacokinetic parameters of perindopril supported by the data of perindoprilat under fasted conditions, it can be concluded that Perindopril tert-butylamine Glenmark 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.

Extrapolation to 2 mg strength
The 2 mg, 4 mg and 8 mg perindopril tablet are completely dose-proportional. The dissolution profiles for all tablet strengths are similar under identical conditions for the 2, 4 and 8 mg tablets. All tablet strengths are manufactured by the same manufacturer and at the same manufacturing site. Therefore the results of the bioequivalence study with the 4 mg and 8 mg tablets also apply to the 2 mg tablets.

Food interaction
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. 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.

The MEB has been assured that the bioequivalence studies have 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 SPC text is similar to the SPC text of product of the innovator in the Netherlands (Coversyl).
In October 2008, the PhVWP has reached consensus with regard to ACE inhibitors and Angiotensin II Receptor Antagonists (AIIRAs) and recommendations on the use during the 1st trimester of pregnancy. As a result of the consensus of the PhVWP, the wording in sections 4.3, 4.4 and 4.6 of the SPC has been adapted to the recommendations of the PhVWP through a type II variation (NL/H/1336/001-003/II/001).

Readability test

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC.

The developed questionnaire contained 19 questions specific to content of the PL and 4 questions with regard to the layout and the patient-friendliness of the PL. The type of the test was an evaluation and problem-seeking test. The test was conducted through one-to-one structured interviews. The technical readability, comprehensibility of the text, traceability of the information and the applicability were investigated.

A pilot round of testing was performed with 3 participants to identify any major changes needed to the PIL. No initial problems were observed. Afterwards the first test-round was performed with 10 participants. This first round of testing reported problem sections of the PIL and suggestions for revisions to the PIL were offered. As a result, the MAH revised some areas of the PIL.

The second test was also performed with 10 participants. The test results of this second round of testing were considered satisfactory. The second test round did not lead to further adaptations of the PIL. The overall conclusion of the readability test is that potential users are able to locate, understand and act appropriately upon the information given in the PIL.

There were sufficient questions about the critical sections of the package leaflet. In the test it was easy to determine which results are linked to which conclusions. The conclusions reflect the results and are clear, concise and clearly presented. The results have been translated into specific recommendations relating to text passages and particular aspects of the text, since the participants, or potential users, of the first testing round were unable to locate, understand and act appropriately upon the information on certain part of the PIL. The patient information leaflet has been adequately adapted.

The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Perindopril tert-butylamine Glenmark 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 Glenmark 2 mg, 4 mg and 8 mg, tablets were authorised in the Netherlands on 26 March 2008.

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 Glenmark 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 25 July 2008.

The PSUR submission cycle is 3 years. The date of the national (Dutch) marketing authorisation of the first Glenmark MA in Europe for perindopril will be considered as data lock point for future PSURs, namely 15 November 2007. Therefore, the data lock point for the first PSUR will be on 15 November 2010.

The date for the first renewal will be: 28 July 2013

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

Quality - active substance

- The MAH committed to submit validation data for microbial contamination of the active substance.

Quality - medicinal product

- The MAH committed that shipping will be in controlled conditions to ensure the product is maintained at the recommended storage conditions. Data loggers will be used with all shipments.
- The MAH committed to validate the first three commercial batches of product of each strength as per the approved process validation protocol as enclosed in the dossier, following launch in the first instance and following scale-up, as applicable, for the larger batch sizes.
- The MAH committed to place the first three commercial batches of all strengths on stability in accordance with the approved protocol. These data will be monitored and if anything unexpected is seen, this will be notified to the Authorities.

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
To implement final agreed wording by PhVWP with regard to pregnancy and lactation in SPC and PIL.	NL/H/1336/ 001-003/II/ 001	II	30-3-2009	29-5-2009	Approval	N
Submission of a new or updated Ph.Eur. Certificate of Suitability for an active substance or starting material/reagent/intermediate in the manufacturing process of the active substance; from a manufacturer currently approved.	NL/H/1336/ 001-003/IA/ 002	IA	23-9-2009	7-10-2009	Approval	N
Change in the name and/or address of the marketing authorisation holder and consequentially Batch Release and QC testing site.	NL/H/1336/ 001-003/IA/ 003	IA	24-9-2009	8-10-2009	Approval	N