

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Perindopril tert-butylamine/Indapamide Mylan
2/0.625 mg and 4/1.25 mg, tablets
Mylan B.V., the Netherlands

perindopril tert-butylamine/indapamide

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/2343/001-002/DC
Registration number in the Netherlands: RVG 109916-109917

6 September 2012

Pharmacotherapeutic group:	perindopril and diuretics
ATC code:	C09BA04
Route of administration:	oral
Therapeutic indication:	2 mg/0.625 mg - essential hypertension; 4 mg/1.25 mg – essential hypertension in patients whose blood pressure is not adequately controlled on perindopril alone.
Prescription status:	prescription only
Date of authorisation in NL:	31 May 2012
Concerned Member States:	Decentralised procedure with BE, ES, FR, IT, LU, CZ (4/1.25 mg strength only)
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/Indapamide Mylan 2/0.625 mg and 4/1.25 mg, tablets from Mylan B.V. The date of authorisation was on 31 May 2012 in the Netherlands.

The product is indicated for treatment of essential hypertension. The 4 mg/1.25 mg product is indicated in patients whose blood pressure is not adequately controlled on perindopril alone.

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

This product is a combination of perindopril tert-butylamine salt, an angiotensin converting enzyme inhibitor, and indapamide, a chlorosulphamoyl diuretic. Its pharmacological properties are derived from those of each of the components taken separately, in addition to those due to the additive synergic action of the two products when combined.

Perindopril is active in all grades of hypertension: mild to moderate or severe. A reduction in systolic and diastolic arterial pressure is observed in the lying and standing position. The antihypertensive activity after a single dose is maximal at between 4 and 6 hours and is maintained over 24 hours. There is a high degree of residual blocking of angiotensin converting enzyme at 24 hours, approximately 80%.

Indapamide, as monotherapy, has an antihypertensive effect which lasts for 24 hours. This effect occurs at doses at which the diuretic properties are minimal. Its antihypertensive action is proportional to an improvement in arterial compliance and a reduction in total and arteriolar peripheral vascular resistance. Indapamide reduces left ventricular hypertrophy.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Preterax® 2 mg/0.625 mg tablets and Bipreterax® 4 mg/1.25 mg tablets which have been authorised in France by Les Laboratoires Servier since 1997. In the Netherlands, Preterax® 2 mg/0.625 mg and 4 mg/1.25 mg have been registered through MRP FR/H/0130/001-002. In addition, reference is made to Preterax/Bipreterax 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 product is compared with the pharmacokinetic profile of the reference product BiPreterax 4 mg/1.25 mg, registered in France. 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 substances

Perindopril tert-butylamine

The active substance perindopril tert-butylamine is an established active substance described in the European Pharmacopoeia (Ph.Eur.*). It's a white or almost white, slightly hygroscopic crystalline powder, which is freely soluble in water and ethanol (96%), and sparingly soluble in methylene chloride.

The CEP procedure is used for perindopril tert-butylamine. 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 active substance specification is considered adequate to control the quality. All methods have been adequately described and are in line with the Ph.Eur. Batch analytical data demonstrating compliance with the specification have been provided for three batches.

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.

** 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.*

Indapamide

Indapamide is an established active substance described in the European Pharmacopoeia. It is a white or almost white powder, which is practically insoluble in water and soluble in ethanol (96%).

The CEP procedure is used for indapamide. 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 specification of indapamide is in line with the CEP. Batch analytical data demonstrating compliance with the drug substance specification has been provided.

Stability of drug substance

The active substance is stable for 30 months when stored under the stated conditions. Assessment thereof was part of granting the CEP.

Medicinal Product

Composition

Perindopril tert-butylamine/Indapamide Mylan 2/0.625 mg is a white, capsule shaped, biconvex, tablet debossed with 'P' to the left of the score and 'TI' to the right of the score on one side of the tablet and 'M' to the left of the score and '1' to the right of the score on the other side of the tablet. The tablet can be divided into equal doses.

Perindopril tert-butylamine/Indapamide Mylan 4/1.25 mg is a white, capsule shaped, biconvex, tablet debossed with 'PTI' on one side of the tablet and 'M2' on the other side.

The tablets are packed in OPA/Al/PVC-Al blister packs and PVC/Aclar-Al blister packs.

The excipients are: hydrophobic colloidal silica, lactose anhydrous, magnesium stearate, microcrystalline cellulose, sodium hydrogen carbonate.

The two strengths are dose proportional.

Pharmaceutical development

Pharmaceutical development was generally satisfactory and addressed issues relating to the drug substances. No novel excipients are used. The rationale for selection of a direct compression process is justified and manufacturing process development is satisfactory. Comparative dissolution profiles of the product versus the EU reference products Bipreterax® tablets and Preterax® obtained from France were generated in three different dissolution media. The dissolution profiles were demonstrated to be similar. Breakability has been demonstrated for the 2/0.625 mg tablets in compliance with the Ph.Eur.

Manufacturing process

The tablets are manufactured by sifting, blending and direct compression. All steps have been adequately described. Given the amount of drug substance in the drug product, the manufacturing process is considered to be a non-standard process. Validation reports of the manufacturing process have been provided for production-scale batches

Control of excipients

All excipients comply with the Ph.Eur. These specifications are acceptable.

Quality control of drug product

The product specifications cover appropriate parameters for this dosage form and include tests for description, identification, dissolution, uniformity of dosage units, assay, water, microbiological test, hardness, friability, related substances and uniformity of mass (for subdivided tablets – 2/0.625 mg only).

The shelf life limit for the individual impurities and total impurities are acceptable with respect to stability data. Validation reports of the analytical methods have been presented and are acceptable. Batch analytical data have been provided for three batches per strength, demonstrating compliance with the specifications.

Stability of drug product

Stability data on the drug product have been provided for three batches of each strength stored at 25°C/60%RH (18 months) and 40°C/75% RH (6 months). The conditions used in the stability studies in cold form and PVC blister packs are according to the ICH stability guideline. The results of a photostability study indicate that the finished product is not photosensitive. The proposed shelf-life of 24 months with the storage condition *Do not store above 25°C* was granted based on the stability data set provided.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose anhydrous is prepared from the milk sourced from healthy animals in the same conditions as milk collected for human consumption. Magnesium stearate is derived from material of vegetable origin and stearic acid used as a raw material is produced from natural palm oil.

II.2 Non-clinical aspects

This product is a generic formulation of Preterax/Bipreterax, which is 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 or indapamide 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 and indapamide are well-known active substances 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/Indapamide 4/1.25 mg (Mylan B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Bipreterax® 4 mg / 1.25 mg tablets (Les laboratoires Servier, France).

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

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 28 healthy male subjects, aged 19-46 years. Each subject received a single dose (4/1.25 mg) of one of the 2 perindopril tert-butylamine/indapamide formulations. There were 2 dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.50, 0.67, 0.83, 1.00, 1.25, 1.50, 2.00, 2.50, 3.00, 4.00, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 72.00 hours after administration of the products.

The design is acceptable for this kind of application. The wash-out and sampling period are long enough and sampling scheme is adequate to estimate pharmacokinetic parameters for perindopril and indapamide.

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

One person withdrew his consent prior to dosing and was replaced before the start of the study. A total of 28 subjects were dosed, but because of one drop-out, 27 subjects completed the study and were included

in pharmacokinetic and statistical analysis. The drop-out happened before dosing of period two and was a result of a THC positive urine scan, which is a protocol violation.

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

Treatment N=27	AUC _{0-t} ng.h/ml	AUC _{0-∞} ng.h/ml	C _{max} ng/ml	t _{max} h	t _{1/2} h
Test	82.8 $\pm$ 26.8	83.9 $\pm$ 26.9	61.2 $\pm$ 18.4	0.67 (0.5-1.0)	1.0 $\pm$ 0.1
Reference	85.1 $\pm$ 30.7	86.2 $\pm$ 30.9	63.1 $\pm$ 21.4	0.67 (0.5-1.0)	0.9 $\pm$ 0.1
*Ratio (90% CI)	0.94 – 1.02	0.94 – 1.02	0.93 – 1.03	--	--
CV (%)	9.7	9.6	10.7	--	--
AUC _{0-∞} 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					

*In-transformed values

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

Treatment N=27	AUC _{0-t} ng.h/ml	AUC _{0-∞} ng.h/ml	C _{max} ng/ml	t _{max} h	t _{1/2} h
Test	--	128.0 $\pm$ 23.4	8.2 $\pm$ 2.0	1.25 (0.83-4.0)	41.7 $\pm$ 12.5
Reference	--	127.9 $\pm$ 26.7	8.9 $\pm$ 2.0	1.5 (0.83-4.0)	45.6 $\pm$ 14.3
*Ratio (90% CI)	--	0.95 – 1.06	0.86 – 0.97	--	--
CV (%)	--	12.3	13.0	--	--
AUC _{0-∞} 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					

*In-transformed values

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

Treatment N=27	AUC _{0-t} ng.h/ml	AUC _{0-∞} ng.h/ml	C _{max} ng/ml	t _{max} h	t _{1/2} h
Test	2814.1 $\pm$ 888.1	2969.1 $\pm$ 989.3	158.3 $\pm$ 38.1	1.5 (0.83-12.0)	15.8 $\pm$ 3.7
Reference	2758.4 $\pm$ 860.4	2989.0 $\pm$ 919.1	142.8 $\pm$ 31.1	2.5 (1.0-5.0)	15.8 $\pm$ 3.8

*Ratio (90% CI)	0.98 – 1.06	0.95 – 1.03	1.04 – 1.18	--	--
CV (%)	8.3	8.7	13.6	--	--
AUC_{0-∞} 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					

**In-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, AUC_{0-∞} 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, perindoprilat and indapamide under fasted conditions, it can be concluded that Perindopril tert-butylamine/Indapamide 4/1.25 mg and Bipreterax® 4 mg / 1.25 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.

A total of 5 mild adverse events were reported in 3 subjects. One subject had increased SGPT, SGOT and blood alkaline phosphatase, another subject experienced hyperglycaemia. For both subjects, the adverse events were considered remotely related to the test formulation. The third subject experienced hyperglycaemia considered remotely related to the reference formulation.

The co-administration of perindopril and indapamide in healthy volunteers and hypertensive patients does not change their pharmacokinetic properties by comparison to separate administration. Following oral administration, perindopril is rapidly absorbed with peak plasma concentrations occurring at about 0.5-1 hour when given under fasting conditions, with an absolute bioavailability of about 75%. Following absorption, 30 to 50% of perindopril is hydrolyzed to perindoprilat, its principal active metabolite, with a mean bioavailability of 25%. Peak plasma concentrations of perindoprilat are attained 3 to 5 hours after perindopril administration. Presence of food does not alter the rate or extent of absorption of perindopril. However, as ingestion of food decreases conversion to perindoprilat by approximately 35%, perindopril tert-butylamine salt should be administered orally in a single daily dose in the morning before a meal. This is stated in the SPC. 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.

Extrapolation to 2 mg/0.625 mg strength

The results of the bioequivalence study with the 4 mg/1.25 mg strength can be extrapolated to the 2 mg/0.625 mg tablets, as both strengths have the same manufacturer, same qualitative composition and same ratio between active substance and excipients. Furthermore, comparable *in vitro* dissolution has been demonstrated both by rapid dissolution and similarity factor calculations

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

The combination of perindopril and indapamide was first approved in 1997, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of perindopril and indapamide 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 approved SPC is broadly in accordance with the agreed SmPC text of Preterax (FR/H/0130/001-002).

Readability test

The package leaflet has not been evaluated via a user consultation study. Instead, a bridging report was provided. The bridging study focused on comparing the two leaflets in the following areas:

- Target patient population
- Key safety messages
- Design and layout issues
- Content issues.

The target patient population is identified as the same for both the parent and daughter PILs. The content of the PILs is broadly similar, and therefore key safety message are not different.

With regard to design and layout issues, the MAH has sufficiently justified that there are no substantial differences between the formats of the two leaflets. In addition, the MAH has successfully tested a number of other leaflets within their product portfolio with this similar house-style. In conclusion, the bridging report is acceptable.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Perindopril tert-butylamine/Indapamide Mylan 2/0.625 mg and 4/1.25 mg, tablets have a proven chemical-pharmaceutical quality and are generic forms of Preterax® 2 mg/0.625 mg and Bipreterax® 4 mg/1.25 mg tablets. Preterax/Bipreterax 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.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Perindopril tert-butylamine/Indapamide Mylan 2/0.625 mg and 4/1.25 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 26 April 2012. Perindopril tert-butylamine/Indapamide Mylan 2/0.625 mg and 4/1.25 mg, tablets were authorised in the Netherlands on 31 May 2012.

The date for the first renewal will be: 31 July 2017.

The following post-approval commitment has been made during the procedure:

Quality - medicinal product

- The MAH committed to place 3 production-scale batches per strength on stability for up to 24 weeks (6 months) at ICH accelerated conditions (i.e. $40 \pm 2^\circ\text{C}/75 \pm 5\% \text{ RH}$) and up to 36 months at ICH long term conditions (i.e. $25 \pm 2^\circ\text{C}/60 \pm 5\% \text{ RH}$).

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 _{1/2}	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