CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Enalaprilmaleaat 40 PCH, 40 mg tablets Pharmachemie B.V., the Netherlands

enalapril maleate

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 34414

25 August 2010

Pharmacotherapeutic group:	ACE inhibitors, plain
ATC code:	C09AA02
Route of administration:	oral
Therapeutic indication:	hypertension; symptomatic heart failure; prevention of symptomatic heart failure in patients with asymptomatic left ventricular disfunction
Prescription status:	prescription only
Date of authorisation in NL:	22 February 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 Enalaprilmaleaat 40 PCH, 40 mg tablets from Pharmachemie B.V. The date of authorisation was on 22 February 2010 in the Netherlands.

The product is indicated for:
- Treatment of hypertension
- Treatment of symptomatic heart failure
- Prevention of symptomatic heart failure in patients with asymptomatic left ventricular disfunction (ejection fraction ≤ 35%).

A comprehensive description of the indications and posology is given in the SPC.
Following oral administration, enalapril is rapidly absorbed and hydrolysed to enalaprilat, a highly specific, long-acting, non-sulphdryl angiotensin-converting enzyme inhibitor. Enalaprilat modulates a specific physiological mechanism, the rennin-angiotensin-aldosterone system, which plays a major role in the regulation of blood pressure. Onset of action begins smoothly and gradually within one hour and the effects continue usually for 24 hours after a single daily dose.
Data indicate no loss of effect during long term therapy. Rebound hypertension does not occur following abrupt cessation of therapy.
Congestive heart failure patients benefit particularly from reduction in pre-load and after-load of the heart, with an increase in cardiac output, without reflex tachycardia.

This national procedure concerns a generic application claiming essential similarity with the innovator product Renitec 40 mg tablets (NL License RVG 10853), which was first registered in the Netherlands on 11 January 1985 by Merck Sharp & Dohme B.V. In addition, reference is made to a previously obtained marketing authorisation for Enalaprilmaleaat 20 PCH (NL RVG 24378) through MRP DK/H/152/004 since September 1999.

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 20 mg product is compared with the pharmacokinetic profile of the reference product Renitec 20 mg tablets, 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 substance
The active substance is enalapril maleate, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). It is a white or almost white crystalline powder, sparingly soluble in water, freely soluble in methanol and practically insoluble in dichloromethane. It dissolves in dilute solutions of alkali hydroxides.

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 active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur., with additional CEP specifications for related substances and residual solvents. The active substance has been sufficiently characterised.

Stability of drug substance
A retest period of 48 months could be granted 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
Enalaprilmaleaat 40 PCH is a white or almost white, round, convex tablet with a score line.
The score line of the tablet is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

The tablets are packed in Polyamide/Al/PVC blisters and unit dose packs.

The excipients are: colloidal anhydrous silica (E551), magnesium stearate (E470b), sodium hydroxide (E524), povidone (E1201), talc (E553b), crospovidone (E1202), cellulose microcrystalline (E460), lactose monohydrate.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. Information on the breakability of the product has not been reported. In view of the SPC in which clearly states that the score line is not to divide tablets into equal halves, this is acceptable.

The MAH refers to a bioequivalence study performed with a corresponding 20 mg product. The 40 mg enalapril maleate tablet is proportional to the 20 mg product. The dissolution profile is similar for the 20, 40 PCH and 20, 40 mg innovator presentations. From a chemical-pharmaceutical point of view, the two dosage strengths are considered essentially similar.
The pharmaceutical development has been described in sufficient detail.

Manufacturing process
The manufacturing process consists of sieving, weighing and dispensing, premixing, preparation of sodium hydroxide solution, preparation of the active ingredient solution, spraying of active ingredient solution, drying, preparation of binder solution, agglomeration and granulation, drying, final blending, sizing, final blending II, compressing and packing. The manufacturing process has been sufficiently validated according to relevant European guidelines.

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, uniformity of mass, disintegration, dissolution rate, friability, resistance to crushing, content uniformity, related substances, assay and microbiological purity. The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site have been provided on two small-scale batches, demonstrating compliance with the release specification. After registration, results of production batches will be submitted.

Stability of drug product
Stability data on the product has been provided for 2 commercial scale batches stored at 25°C/60% RH (36 months), 30°C/65% RH (12 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 OPA-Alu/PVC-Alu blisters. Only for related substances an increasing trend was observed.
Based on the stability data provided, the proposed shelf-life of 3 years could be granted for the drug product, when stored below 30°C in the original package to protect from light and moisture.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose is the only excipient of animal origin. A declaration is included that the milk used for manufacturing lactose is sourced from healthy animals under the same conditions as milk collected for human consumption.

II.2 Non-clinical aspects

This product is a generic formulation of Renitec, 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 enalapril maleate 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

Enalapril maleate is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH has submitted two bioequivalence studies in which the pharmacokinetic profile of the test product Enalaprilmaleaat 20 PCH, 20 mg tablets is compared with the pharmacokinetic profile of the reference product Renitec 20 mg tablets (MSD, 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. The reference product from the French market is identical with Renitec registered in The Netherlands
The formula and preparation of the bioequivalence batch is comparable to the formula proposed for marketing.

Bioequivalence study I
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 12 healthy subjects, aged 25-30 years. Each subject received a single dose (20 mg) of one of the 2 enalapril formulations. The tablet was orally administered with 150 ml water after a fasting period of 12 hours. The volunteers were allowed to eat a standard meal 2 hours after drug administration. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24 and 48 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
All 12 subjects completed the study and were included in the analysis.

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

Treatment N=12	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	616.02 ± 168.43	659.61 ± 157.49	65.78 ± 34.89	3.58 (3-6)	5.57 ± 1.75
Reference	629.09 ± 135.54	662.45 ± 124.47	64.33 ± 23.47	3.50 (2-6)	5.63 ± 1.73
***Ratio (90% CI)**	0.97 (0.90-1.04)	0.99 (0.93-1.05)	0.96 (0.83-1.12)	--	--
CV (%)	10	9	21	--	--

$AUC_{0-\infty}$ 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*

Bioequivalence study II
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 28 healthy subjects, aged 19-45 years. Each subject received a

single dose (20 mg) of one of the 2 enalapril formulations. The tablet was orally administered with 150 ml water after a fasting period of 10 hours. The first meal was served 3 hours after administration of the products. There were 2 dosing periods, separated by a washout period of 10 days.

Blood samples were collected pre-dose and at 1, 2, 3, 4, 6, 8, 12, 24, 48, 72 and 96 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
Twenty-four subjects completed all study periods and were eligible for pharmacokinetic analysis.

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

Treatment N=24	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	672.51 ± 280.92	698.10 ± 284.38	73.28 ± 36.19	3 (2-8)	4.96 ± 2.25
Reference	606.19 ± 188.33	633.41 ± 192.53	65.18 ± 29.71	3.5 (2-6)	5.33 ± 2.39
***Ratio (90% CI)**	0.98 (0.83-1.16)	1.00 (0.87-1.14)	0.98 (0.80-1.19)	--	--
CV (%)	36	28	42	--	--

$AUC_{0-\infty}$ 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 enalaprilate under fasted conditions, it can be concluded that Enalaprilmaleaat 20 PCH and Renitec 20 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 40 mg tablet
The 20 and 40 mg tablets are dose proportional. Both tablets are made by the same manufacturer. The 20 mg formulation has been registerd under RVG 24378. The pharmacokinetics of the active substance are linear, and the dissolution profiles are comparable. The results of the bioequivalence study performed with the 20 mg tablet therefore apply to the 40 mg tablets as well.

Enalapril may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of enalapril. 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.

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

Enalapril was first approved in 1985, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of enalapril 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 national procedure is in accordance with that accepted for the reference product Renitec marketed by MSD.

Readability test

The package leaflet has not been evaluated via a user consultation study. This is acceptable, as the PIL text is almost identical to the ones for the 5, 10 and 20 mg strengths (RVG 24376-24378), which have been determined during the MRP procedure DK/H/152. Readability for this PIL has been established and therefore a waiver can be applied to the 40 mg PIL.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Enalaprilmaleaat 40 PCH, 40 mg tablets has a proven chemical-pharmaceutical quality and is a generic form of Renitec 40 mg tablets. Renitec 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 and are in agreement with other enalapril containing products.

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. Enalaprilmaleaat 40 PCH, 40 mg tablets was authorised in the Netherlands on 22 February 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