

**PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands**

**Enalaprilmaleaat/Hydrochloorthiazide 20/12.5, tablets,
Hexal AG, Germany**

enalapril maleate/hydrochlorothiazide

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/1096/001/MR
Registration number in the Netherlands: RVG 34510**

18 June 2009

Pharmacotherapeutic group:	ACE inhibitors and diuretics
ATC code:	C09BA02
Route of administration:	oral
Therapeutic indication:	Essential hypertension
Prescription status:	prescription only
Date of first authorisation in NL:	30 October 2006
Concerned Member States:	Mutual recognition procedure with DE, EE, HU, IT, LT, LV, PL
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 Enalaprilmaleaat/Hydrochlorothiazide 20/12.5, 20 mg/12.5 mg tablets, from Hexal AG. The date of authorisation was on 30 October 2006 in the Netherlands.

The product is indicated for essential hypertension. This fixed dose combination is indicated in patients whose blood pressure is not adequately controlled with enalapril alone. This fixed dose may also replace the combination of 20 mg enalapril maleate and 12.5 mg hydrochlorothiazide in patients who have been stabilised on the individual active substances given in the same proportions as separate medications. This fixed dose combination is not suitable for initial therapy.

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

Enalaprilmaleat/hydrochlorothiazide 20 mg/12.5 mg is a combination of an angiotensin-converting enzyme inhibitor (enalapril) and a diuretic (hydrochlorothiazide).

Enalapril maleate is the maleate salt of enalapril. Angiotensin converting enzyme (ACE) is a peptidyl dipeptidase which catalyses the conversion of angiotensin I to the pressor substance angiotensin II. After absorption, enalapril is hydrolysed to its active metabolite enalaprilat, which inhibits ACE. Inhibition of ACE results in decreased plasma angiotensin II, which leads to increased plasma rennin activity (due to removal of negative feedback of rennin release), and decreased aldosterone secretion.

ACE is identical to kininase II. Thus enalapril may also block the degradation of bradykinin, a potent vasodepressor peptide. However, the role that this plays in the therapeutic effects of enalapril remains to be elucidated.

Hydrochlorothiazide is a thiazide diuretic which acts as by inhibiting fluid-expelling and blood pressure-lowering agent which increase the tubular re-absorption of sodium in the cortical diluting segment.

It increases the urinary excretion of sodium and chloride and, to a lesser degree, the excretion of potassium and magnesium, thus increasing diuresis and exerting an anti-hypertensive effect.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Co-Renitec 20/12.5 mg (NL RVG 11825) which has been registered in the Netherlands by Merck Sharp & Dohme B.V. since 1988 (original product). In addition, reference is made to Co-Renitec authorisations in the individual member states (reference product).

Co-Renitec 20/12.5 mg approved in The Netherlands is used as EU-reference product for the application in LT, LV, PL, RO and SI, as Co-Renitec does not have a marketing authorisation in these CMSs. Information about this EU-reference product was provided to these CMSs.

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 Co-Renitec, registered in Austria. 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.

No paediatric development programme has been submitted.

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.

For manufacturing sites within the Community, the member states have accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the member states have accepted information issued by the inspection services of the competent authorities within the Community, as certification that acceptable standards of GMP are in place at those non-Community site.

Active substance

Enalapril maleate

General information

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. As the active substance is dissolved during manufacture of the drug product, polymorphism and particle size are not relevant.

The Active Substance Master File (ASMF) procedure is used for the only supplier. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

In the DMF the drug substance has been adequately characterized. In general sufficient information has been provided on the synthesis.

Quality control of drug substance

The drug substance specification is in line with the Ph.Eur., with additional requirements for residual solvents and single unknown impurity. The specifications are acceptable in view of the Ph.Eur. and the ICH Guidelines.

Stability of drug substance

A re-test of three years is founded by long term and accelerated stability data included in the DMF.

Hydrochlorothiazide

General information

The active substance is hydrochlorothiazide, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). It is a white or almost white, crystalline powder, very slightly soluble in water, soluble in acetone, and sparingly soluble in alcohol. It dissolves in dilute alkali hydroxides. Polymorphism is not known for hydrochlorothiazide. A requirement for particle size has been set.

The CEP procedure is used for the active substance Hydrochlorothiazide. 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, and 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 Ph.Eur. For all suppliers a valid Certificate of Suitability has been provided.

Quality control of drug substance

The drug substance specification is in line with the Ph. Eur., with additional requirements for residual solvents, any single unknown and particle size. The specifications are acceptable in view of the Ph. Eur. and ICH Guidelines.

Stability of drug substance

For all suppliers adequate re-test periods of 3-5 years have been defined based on the re-tests given in the respective CEP's and if applicable based on additionally submitted stability data.

** 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/Hydrochloorthiazide 20/12.5 contains as active substance 20 mg of enalapril maleate and 12.5 mg of hydrochlorothiazide, and are white oval, biconvex snap tap tablets, scored on one side, and embossed with "E H" on the other side.

The excipients are: calcium hydrogen phosphate (dihydrate), lactose monohydrate, magnesium stearate, maize starch, sodium hydrogen carbonate, talc.

All excipients are well known, commonly used substances, included in the Ph.Eur.

Package

The tablets are packed in laminated aluminium-polyamide/Al/PVC blisters. The secondary packaging consists of cardboard carton.

The packaging is a blister composed of aluminium foil with internal and external lacquer heatsealed to polyamide/Al/PVC foil. The internal lacquer is heatsealed to the PVC. Acceptable specifications and quality references are included for both foils, including reference IR spectra for both plastics.

The MAH has provided a declaration that the packaging materials comply with the Ph.Eur. and EU guideline 90/128/EU.

Pharmaceutical development

The objective was to develop a product that would be essentially similar to the innovator product Co-renitec® 20/12.5 mg by MSD.

Because of the ease of handling and the dosage accuracy tablets were chosen as the preferred dosage form. The tablets are equipped with a "snap tap" in order to improve breakability. The MAH has performed the Ph.Eur. test for uniformity of mass of single dose preparations (Ph.Eur. 2.9.5) on the divided tablets. In view of the Ph.Eur. requirements, the results were acceptable.

Clinical formulations

Bioequivalence testing was performed comparing an Enalaprilmaleaat/Hydrochloorthiazide 20/12.5 batch to a Co-renitec® 20/ 12.5 mg batch from the Austrian market. It is noted that the composition of the bio-batch corresponds to the currently proposed composition, however two minor differences are reported:

1. Instead of the proposed appearance (oval biconvex snap tap) the former appearance was used (round/ biplane)

2. the calcium hydrogen phosphate that was used in the bio-batch was used in the anhydrous form (and tested in accordance with the USP) while in the proposed composition the hydrate form is proposed (and is tested in accordance with the Ph.Eur.).

In view of the rapid dissolution ($\geq 80\%$ after 30 minutes) of both substances in the bio-batch and in the current batches, the difference in tablet appearance is deemed acceptable. The difference in hydrate forms of calcium hydrogen phosphate that is used is deemed irrelevant in view of the proposed manufacturing process. The calcium hydrogen phosphate is mixed with water-containing granulation liquid, as a result the anhydrous form will become hydrated too.

The bio-batch is manufactured at a manufacture site, which is different from the proposed manufacture sites. The process is however the same. Dissolution profiles are included for batches from both manufacturing sites. In comparison with the dissolution profiles from the biobatch and the innovator product (Co-renitec®) similar profiles were obtained for both active substances. The dissolution results of the tested batches gave comparative results. In addition, it can be noted that all batches complied with the drug product specification.

In addition, the MAH has presented dissolution profiles in which the innovator products from several member states, i.e. BE, DK, ES, FR, IT, IE, SE, FI, UK, GR, PO, were compared with the reference product that was used in the bio-equivalence testing. The dissolution characteristics were deemed adequate.

The method for dissolution for enalapril maleate is conform the method of the USP Monograph Enalapril and Hydrochlorothiazide Tablets and agreed. The method for dissolution for hydrochlorothiazide does not conform to that method, but uses the same medium (0.1 N hydrochloric acid) and rotation speed (100 rpm) as the method of the USP Monograph Hydrochlorothiazide Tablets, with a tighter requirement ($Q=80\%$ within 30 minutes), yet with a different apparatus (paddle instead of basket). Sink conditions can be considered. The set specifications for dissolution are acceptable in view of the dissolution profile of the bio-batch.

Manufacturing process quality control of the medicinal product

The product is manufactured by wet granulation where enalapril maleate is dissolved in the granulation liquid. The manufacture has been described in sufficient detail. Validation has been performed on 3 industrial batches for both manufacture sites. Adequate in-process controls are stated, accompanied with acceptable requirements including loss on drying of the granulate and the precompression blend and testing of tablet hardness. The process can be regarded as validated.

Quality control of the medicinal product

The product specification for the drug product includes tests for appearance, uniformity of dosage units, tablet hardness, water content, identity, assay, dissolution and related substances of both active substances, disintegration and microbial quality. For shelf life wider limits for related substances are applied. The requirements are acceptable.

Batch analysis data have been provided of production batches from both manufacture sites. All results complied with the specifications and no significant differences were found between the different batches.

For most methods reference is made to the Ph.Eur.. For the methods that are used for Assay, Purity and Dissolution the MAH has provided a description of the analytical method including adequate validation.

The MAH provided 3 batches from one proposed production site, and 3 pilot scale batches and 3 production scale batches from the other proposed production site. All batches demonstrated compliance with the specification. No significant differences were found between the different batches.

Breakability

The tablets bear a score line. The tablets of two batches have been broken by hand into two pieces. Both batches complied with the test for uniformity of mass of single dose preparations (Ph Eur 2.9.5.). None of the halved tablets was outside 85-115%. In view of that, the tablets comply with the requirement as stated in the Ph Eur Monograph Tablets.

Stability tests on the finished product

A shelf life of 3 years, when stored below 30°C has been justified with long term, intermediate and accelerated stability data of pilot-scale batches. During storage degradation products increase, more pronounced at accelerated than at normal and intermediate conditions. Only at accelerated conditions out of specification results are encountered. In view of this, the applied storage condition is required. The MAH has committed to perform stability studies with production scale batches.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

The MAH has provided TSE certificates for the excipients magnesium stearate and lactose monohydrate. It is stated that the magnesium stearate is 100% of vegetable origin. For lactose monohydrate adequate certificates have been provided that the milk that is used in the production of the lactose is sourced from healthy animals in the same conditions as applied when milk is collected for human consumption (EMA/410/01/rev1). Additionally it is declared that the only ruminant material that is used in the production is calf rennet. The calf rennet is in accordance with public statement EMA/CPMP/571/02. The provided certifications are deemed adequate.

II.2 Non clinical aspects

This product is a generic formulation of Co-Renitec 20/12.5 mg, 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 or hydrochlorothiazide 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 and hydrochlorothiazide are well-known active substances with established efficacy and tolerability.

For this generic application, the MAH has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Enalaprilmaleaat/Hydrochlorothiazide 20/12.5, tablets is compared with the pharmacokinetic profile of the Austrian reference product Co-renitec 20/12.5 mg tablets.

Design

A two-way, single-dose, randomised crossover bioequivalence study was carried out under fasted conditions in 32 healthy male subjects, aged 18-45 years. Each subject received a single dose (20/12.5 mg) of one of the 2 enalapril maleate/hydrochlorothiazide formulations. The tablet was orally administered with 200 ml water after a 12 hour fasting period. There were 2 dosing periods, separated by a washout period of 14 days. Blood samples were collected predose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 24, and 48 hours after administration of the products.

Plasma samples were analysed for enalaprilat (the active metabolite) with a radio-immuno-assay procedure, which was specific for enalaprilat, and for hydrochlorothiazide with HPLC and UV detection. The methods were validated and a validation report was provided. All subjects completed the bioequivalence study and were eligible for pharmacokinetic analysis. The statistical analysis was adequate.

Results

The pharmacokinetic variables of enalaprilat and hydrochlorothiazide of the test tablet and reference are shown in the tables below: AUC_(0-inf.), C_{max}, t_{max} and t_{1/2} as mean ± s.d.;

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

Treatment N=32	AUC _{0-t} ng.h/ml	AUC _{0-∞} ng.h/ml	C _{max} ng/ml	t _{max} h	t _{1/2} h
Test	792 \pm 163	808 \pm 164	98 \pm 22	3.2 \pm 0.6	8.8 \pm 1.6
Reference	738 \pm 165	757 \pm 165	88 \pm 19	3.3 \pm 0.5	9.7 \pm 2.5
*Ratio (90% CI)	-	1.07 (1.02-1.12)	1.11 (1.04-1.16)	-	-
CV (%)	-	10.3	12.3	-	-
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 hydrochlorothiazide under fasted conditions.

Treatment N=32	AUC _{0-t} ng.h/ml	AUC _{0-∞} ng.h/ml	C _{max} ng/ml	t _{max} h	t _{1/2} h
Test	437 \pm 91	479 \pm 100	70 \pm 17	2.1 \pm 0.9	6.7 \pm 2.3
Reference	430 \pm 90	468 \pm 99	73 \pm 15	1.8 \pm 0.8	6.3 \pm 2.0
*Ratio (90% CI)	-	1.03 (0.96-1.09)	0.96 (0.89-1.04)	-	-
CV (%)	-	14.3	18.0	-	-
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*

Conclusion and discussion

The 90% confidence intervals calculated for 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 enalaprilat (the active metabolite of enalapril) and hydrochlorothiazide under fasted conditions, it can be concluded that Enalaprilmaleaat/Hydrochlorothiazide 20/12.5 tablets and Co-renitec 20/12.5 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.

However, during the mutual recognition procedure no consensus was reached at day 90 regarding the bioequivalence study and the package leaflet. Therefore, the procedure was referred to the CMD(h) for the following items:

- 1) The opinion in the EU is that for establishing bioequivalence between innovator and generic products the parent compound should be evaluated whenever this is technically feasible, i.e. the parent compound is sufficiently detectable in blood.
- 2) The pictogram and text give the impression that there is a dose recommendation for ½ a tablet, but there is no such recommendation. This may confuse prescribing physicians and patients. The only acceptable dosage recommendation of the fixed dose for all patients is 1 tablet per day or a dose titration with the individual components.

The referral has been discussed in the CMD(h) of February 2008. At the CMD(h) meeting the RMS presented its view and the MAH's written response was discussed. There was a discussion on whether bioequivalence should be demonstrated only on the active metabolite enalaprilat data, or whether bioequivalence should also be demonstrated on the parent compound enalapril. In Europe a decision was earlier made that parent compound data are strongly preferred instead of the metabolite data in bioequivalence studies. However, in this bioequivalence study the metabolite was measured. The RMS agrees with the performed procedure as the product has been approved in The Netherlands before there was a decision in Europe.

The MAH made a post-approval commitment to perform an additional single dose fasten BE-study on the parent compound.

The SPC and Package Leaflet were adapted regarding information about the score line.

A positive opinion was adopted on 3 March 2008.

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

In view of the existing knowledge and experience with the active substances enalapril maleate and hydrochlorothiazide, the available data and the known risk-benefit profile, it is accepted that the MAH will perform standard pharmacovigilance activities as described in volume 9 of *The rules governing medicinal products in the European Union*. An additional Risk Management Plan and Risk Minimisation Plan are not required at the moment. If, in the future, new data suggest differently the submission of a Risk Management Plan and a Risk Minimisation Plan can be necessary.

Product information

SPC

The SPC is satisfactory from a clinical, preclinical and pharmaceutical point of view. The template is in accordance with the latest QRD version.

Readability test

A readability test was performed in August 2006. The test consisted of a pilot round and three test rounds. The pilot was performed with 5 participants, test round one and two were performed with 10 participants, and test round three was performed with 20 participants. Fourteen questions were asked about the package leaflet. Furthermore, three more general questions about the package leaflet were asked. The questions cover the most important and critical parts of the package leaflet.

Most of the recommendations after the pilot, first and second test concern the lay-out. After each test the lay-out has been adapted.

After the final (third) test it was concluded that the revised design of the information made all the difference in performance, and findability improved to an acceptable level. A general comment in the report is that in principle such a large leaflet has very little chance of being actually read by the patient. However, as the SPC contains a lot of information (information about two active ingredients), it is difficult to draw up a small package leaflet.

The conclusions reflect the result of the test. The conclusions are clear, concise and clearly presented.

The package leaflet has been adapted sufficiently taking into account the results of the test.

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Attention was paid to the three most important quality aspects: traceability, comprehensibility and applicability.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Enalaprilmaleaat/Hydrochloorthiazide 20/12.5, 20 mg/12.5 mg tablets have a proven chemical-pharmaceutical quality and are a generic form of Co-Renitec 20/12.5 mg. Co-Renitec 20/12.5 mg 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 SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors. Enalaprilmaleaat/Hydrochloorthiazide 20/12.5, tablets was authorised in the Netherlands on 30 October 2006.

During the mutual recognition procedure no consensus was reached at day 90 regarding the bioequivalence study and the package leaflet. In the CMD(h) meeting of 18 and 19 February 2008, the following was discussed:

Bioequivalence was demonstrated on the basis of the metabolite data, and not on the basis of the parent. There was a discussion on whether bioequivalence should be demonstrated only on the active metabolite enalaprilat data, or whether bioequivalence should also be demonstrated on the parent compound enalapril. In Europe a decision was made that parent compound data are strongly preferred instead of the metabolite data in bioequivalence studies. However, the the product was registered in the Netherlands before this decision was made.

- The MAH made a post-approval commitment to perform an additional single dose fasten BE-study on the parent compound.
- The pictogram and text in the SPC and Package Leaflet give the impression that there is a dose recommendation for ½ a tablet, but there is no such recommendation. This may confuse prescribing physicians and patients. The SPC and Package Leaflet were adapted regarding information about the score line.

The concerned member states, on the basis of the data submitted, considered that bioequivalence has been demonstrated for Enalaprilmaleaat/Hydrochloorthiazide 20/12.5, 20 mg/12.5 mg tablets, with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 3 March 2008.

A European harmonised birth date has been allocated (24-03-2002) and subsequently the first data lock point for enalapril maleate/hydrochlorothiazide is November 2009. The first PSUR will cover the period from October 2006 to November 2009, after which the PSUR submission cyclis is 3 years.

The date for the first renewal will be: 31 July 2010.

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

Quality

- The MAH committed to perform stability studies with production scale batches.

Clinical

- The MAH committed to perform an additional single dose fasten BE-study on the parent compound.

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
Change in the name and/or address of a manufacturer of the finished product	NL/H/1096/001/IA/001	IA	29-04-2008	13-05-2008	Approval	N