PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands

Quinapril 40 mg, film-coated tablets
Stada Arzneimittel AG, Bad Vilbel, Germany

quinapril (as hydrochloride)

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/0819/001/MR
Registration number in the Netherlands: RVG 29866

Date of first publication: 22 July 2009
Last revision: 29 August 2011

Pharmacotherapeutic group: ACE inhibitors, plain
ATC code: C09AA06
Route of administration: oral
Therapeutic indication: essential hypertension, and congestive heart failure
Prescription status: prescription only
Date of authorisation in NL: 10 February 2005
Concerned Member State: Mutual recognition procedure with BE
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 concerned member state has granted a marketing authorisation for Quinapril 40 mg from Stada Arzneimittel AG. The date of authorisation was on 10 February 2005 in the Netherlands.

The product is indicated for essential hypertension, and congestive heart failure.

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

Quinapril is a long-acting angiotensin converting enzyme (ACE) inhibitor, which exhibits similar pharmacodynamic properties as other ACE inhibitors such as lisinopril and ramipril. It inhibits the conversion relatively inactive angiotensin I to the active angiotensin II, which plays a role in hypertension and heart failure. Quinapril is hydrolysed after absorption to form its major active metabolite quinaprilat.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Acupril®, containing 43.4 mg quinapril hydrochloride. The innovator product has been registered in the Netherlands by Pfizer since 3 August 1990 for the 5, 10 and 20 mg strengths (NL License RVG 13601, 13602, 13603), whereas the 40 mg strength has been registered since 5 July 1996 (NL License RVG 19839). In addition, reference is made to Acupril authorisations in BE (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 applicant has submitted one bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the Spanish reference product, Acuprel 40 mg tablets, by Pfizer B.V. registered in Spain. Acuprel is the name for the innovator’s product in Spain. 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 preclinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to this product.
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 authorisations.

Active substance

General information
The active substance is quinapril hydrochloride. There is no Ph.Eur.* monograph on quinapril, but a draft monograph has been published in the USA Pharmacopoeial Forum (Volume 25, Number 4, July-Aug. 1999). This draft has been used as a guideline.

Manufacture
The Active Substance Master File (ASMF) procedure is used for the active substance. 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/EMEA 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.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for 3 production batches.

Stability of drug substance
Stability data on the active substance have been provided for 9 batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 4 years, when stored at 2-8°C.

* 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
Quinapril 40 mg film-coated tablets contain 40 mg quinapril.
The quinapril 40 mg tablets are reddish brown in colour and round.
The tablets are supplied in Alu/Alu blisters. The blister are packaged in a cardboard box.

The excipients are: magnesium carbonate (E504), hydroxypropylcellulose (E463), crospovidone, magnesium stearate (E470b), methacrylate copolymer (Eudragit E), titanium dioxide (E171), talc (E553b), macrogol, and iron oxide (E172).

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

The objective was to develop a product that would be bioequivalent with the Acuprel 40 mg, marketed by Pfizer B.V.
The excipients used are common in the manufacture of conventional immediate-release tablets. All excipients comply with the requirements laid down in their respective Ph.Eur. monographs, except for hydroxypropylcellulose, iron oxide and the coating material Eudragit. For hydroxypropylcellulose the USP specifications were used, whereas for iron oxide and Eudragit in-house specifications were provided.

Manufacturing process and quality control of the medicinal product
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for 3 pilot batches in accordance with the relevant European guidelines. The MAH committed to provide process validation data of the first 3 full-scale batches.

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specifications include tests for appearance, identification, average tablet mass, uniformity of mass, dimensions, disintegration, dissolution, water, assay, residual solvents, related substances and microbial purity. Limits in the specifications have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data for 3 tablet batches have been provided, demonstrating compliance with the specification.

Stability tests on the finished product
Stability data on the product have been provided for 3 batches in accordance with applicable European guidelines demonstrating the stability of the product for 3 years when stored in the original packaging in order to protect from humidity, and not above 25°C.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non-clinical aspects

This product is a generic formulation of Acupril, 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 identical products on the market. The approval of this product will not result in an increase in the total quantity of quinapril 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

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

For this generic application, the MAH has submitted one bioequivalence study, which compares the Quinapril 40 mg tablet to the Spanish reference product, Acuprel® 40 mg tablet.

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 concerned member states.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study
A randomised, single-dose, 2-way cross-over, bioequivalence study was carried out under fasted conditions in 36 healthy volunteers. Eighteen males and 18 females, aged 19-29 years, were included in the study. Each subject received daily a single dose (40 mg) of one of the 2 quinapril formulations. The tablet was orally administered with 200 ml water after an overnight fast. For each subject there were 2 dosing periods, separated by a washout period of 14 days.

Blood samples were collected immediately before dosing and on the following times after dosing: 20, 40, 60, 80, 100, 120, 150 minutes and 3, 4, 6, 8, 10, 12, and 24 hours (a total of 15 samples).

The analytical method is adequately validated and considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

From the literature it is well known that the absorption of quinapril is not affected by food. The tablets should be swallowed with a glass of water. Therefore, 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.

Results
All subjects completed the study and were eligible for pharmacokinetic evaluation.

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC(_{0-t})</th>
<th>AUC(_{0-\infty})</th>
<th>C(_{\text{max}})</th>
<th>( t_{\text{max}} )</th>
<th>( t_{1/2} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>393 ± 173</td>
<td>403 ± 174</td>
<td>408 ± 251</td>
<td>0.7 (0.3-2.0)</td>
<td>0.9 ± 0.2</td>
</tr>
<tr>
<td>Reference</td>
<td>383 ± 144</td>
<td>390 ± 144</td>
<td>363 ± 169</td>
<td>0.7 (0.3-2.0)</td>
<td>1.0 ± 4.0</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>1.01 (0.94-1.09)</td>
<td>1.02 (0.95-1.10)</td>
<td>1.05 (0.91-1.21)</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>CV (%)</td>
<td>18.3</td>
<td>18.0</td>
<td>38</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

\( \text{AUC}_{0-\infty} \) area under the plasma concentration-time curve from time zero to infinity
\( \text{AUC}_{0-t} \) area under the plasma concentration-time curve from time zero to \( t \) hours
\( C_{\text{max}} \) maximum plasma concentration
\( t_{\text{max}} \) time for maximum concentration
\( t_{1/2} \) half-life
* in-transformed values

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC(_{0-t})</th>
<th>AUC(_{0-\infty})</th>
<th>C(_{\text{max}})</th>
<th>( t_{\text{max}} )</th>
<th>( t_{1/2} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>4198 ± 946</td>
<td>4294 ± 972</td>
<td>1207 ± 345</td>
<td>1.3 (1.0–4.0)</td>
<td>2.1 ± 0.3</td>
</tr>
<tr>
<td>Reference</td>
<td>3921 ± 1026</td>
<td>4021 ± 1055</td>
<td>1094 ± 297</td>
<td>1.7 (1.0–4.0)</td>
<td>3.3 ± 1.5</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>1.08 (1.03-1.12)</td>
<td>1.08 (1.03-1.12)</td>
<td>1.10 (1.03-1.17)</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>
The 90% confidence intervals calculated for \( \text{AUC}_{0-t} \), \( \text{AUC}_{0-\infty} \) and \( C_{\max} \) are within the bioequivalence acceptance range of 0.80 – 1.25. The statistical analysis of the pharmacokinetic data was adequate. Based on the pharmacokinetic parameters of both quinapril and quinaprilat under fasted conditions, it can be concluded that test Quinapril 40 mg tablet and the Spanish reference Acuprel 40 mg tablet are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

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**

Quinapril was first approved in 1989 in the European Union, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of quinapril 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 Risk Management Plan is not necessary for this product.

**Product information**

**SPC**

The content of the SPC approved during the mutual recognition procedure is in accordance with the SPC of the innovator product.

**Readability test**

The package leaflet has been evaluated via an user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The questionnaire contained three types of questions: on findability (where the participant had to point to the section in the PL where he/she could find the answer to the question), comprehensibility (where the participant had to give the answer to the question in his/her own words) and usability (where the participant was asked what to do in special situations).

A first test was performed with 10 participants. This led to several general recommendations and a number of suggestions for improving findability, comprehensibility and usability. The second test with the adapted text was performed with 10 participants. In the first test round, a total of 73% of the questions were answered correctly. The changes made after the first test round improved this readability to 83%. No new problems were identified in this test round. For this reason, the text of the PL was not adapted after the second test round.

In the test it was easy to determine which results are linked to which conclusions. The conclusions reflect the result and are clear, concise and clearly presented. The results have been translated into sufficient specific recommendations relating to text passages and particular aspects of the text. The patient information leaflet has been adapted sufficiently taking into account the results of the test.
III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Quinapril 40 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Acupril. Acupril 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 is consistent with that of the innovator product.

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. Braille conditions are met by the MAH.

The Board followed the advice of the assessors. Quinapril 40 mg, film-coated tablets were authorised in the Netherlands on 10 February 2005.

There was no discussion in the CMD(h). Agreement between the member states was reached during a written procedure. The mutual recognition procedure was finished on 22 September 2006. The concerned member state, on the basis of the data submitted, considered that bioequivalence has been demonstrated for Quinapril 40 mg tablets with the reference product, and has therefore granted a marketing authorisation.

The first PSUR will be submitted within 60 days after the data lock point (DLP) in September 2009. The second PSUR will have a DLP in April 2011 (according to the EU HBD project). Hereafter, the PSURs will be submitted three-yearly.

The renewal application, with an early common renewal date of 31 May 2010, was submitted together with the first PSUR. Hereafter renewal was granted with unlimited validity. See annex I on page 10.

The following post-approval commitments were made during the procedure:

Quality – Medicinal product
- The MAH committed to provide further process validation data of the first 3 full-scale batches. This commitment has been fulfilled on February 2010.
- The MAH committed to submit a type II variation for the procedure SE/H/0392 in order to harmonise this SmPC with the SmPC of the procedure NL/H/0819/01/MR with regard to the indication ‘congestive heart failure’. This type II variation has to be submitted as soon as possible after the finalisation of the MRP, but not later than 3 November 2006. This commitment has been fulfilled. See variation SE/H/0392/001-004/II/005 in the ‘Steps taken after finalisation of the initial procedure’ table on page 8.
## STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Type of modification</th>
<th>Date of start of the procedure</th>
<th>Date of end of the procedure</th>
<th>Approval/n on approval</th>
<th>Assessment report attached</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in pack size of the finished product. Change in the number of units (e.g. tablets, ampoules, etc.) in a pack. Change outside the range of the currently approved pack sizes.</td>
<td>NL/H/0819 /001/IB/001</td>
<td>IB</td>
<td>8-11-2006</td>
<td>14-12-2006</td>
<td>Approval</td>
<td>N</td>
</tr>
<tr>
<td>Change in the name and/or address of the marketing authorisation holder.</td>
<td>NL/H/0819 /001/IA/002</td>
<td>IA</td>
<td>23-1-2007</td>
<td>13-2-2007</td>
<td>Approval</td>
<td>N</td>
</tr>
<tr>
<td>Documentation as a result of the post-approval commitment: type II variation for the procedure SE/H/0392/001-004 in order to harmonise this SmPC with the SmPC of NL/H/0819/001/MR concerning the indication 'congestive heart failure'.</td>
<td>SE/H/0392 /001-004/II/005</td>
<td>PAC</td>
<td>1-1-2007</td>
<td>26-4-2007</td>
<td>Approval</td>
<td>N</td>
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<tr>
<td>Update DMF Quinapril hydrochloride from Farmhispania S.A.</td>
<td>NL/H/0819 /001/II/003</td>
<td>II</td>
<td>23-10-2009</td>
<td>25-2-2010</td>
<td>Approval</td>
<td>N</td>
</tr>
<tr>
<td>Renewal of the marketing authorisation.</td>
<td>NL/H/0819 /001/R/001</td>
<td>Renewal</td>
<td>27-3-2010</td>
<td>25-2-2011</td>
<td>Approval</td>
<td>Y, Annex I</td>
</tr>
</tbody>
</table>
Annex I - Variation NL/H/819/001/R/001 – Renewal of the marketing authorisation

I RECOMMENDATION

Based on the review of the data submitted for this renewal application, the benefit/risk balance of Quinapril 40 mg (quinaprilhydrochloride), film-coated tablets, NL/H/0819/001 remains positive.

The RMS therefore recommends the renewal of the Marketing Authorisation for Quinapril 40 mg, provided that the SPC and PL will be updated as requested. The renewal can be granted with unlimited validity.

II SCIENTIFIC DISCUSSION

II. 1 Introduction

Quinapril filmcoated tablets contain 40 mg quinaprilhydrochloride. Quinapril is a non-sulphhydryl angiotensin-converting enzyme inhibitor. In this report the Periodic Safety Update Report covering the period 22 September 2006 to 22 September 2009 is assessed.

II.2 Module 1/GMP compliance statements

The RMS has been assured that acceptable standards of GMP are in place for these product types at all of the sites responsible for the manufacture and assembly of this product prior to granting its national authorisation.

Together with the application of this renewal, a copy of the current GMP certificate has been submitted issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at the manufacturing site responsible for batch release, for batch control/testing and for primary and secondary packaging within the Community.

Together with the application of this renewal, the MAH submitted certifications that acceptable standards of GMP are in place at the manufacturing site of the bulk tablets in Spain.

Manufacturer active ingredient
Taking into account the review 2001, a new requirement is a GMP declaration that the active ingredient is produced in accordance with the GMP requirements.
The qualified person of the manufacturer responsible for batch release, declared that the active ingredient is produced in accordance with the GMP-requirements. In addition, the qualified person of the manufacturer of the bulk tablets, declared that the active ingredient is produced in accordance with the GMP-requirements.

In October 2009, the MAH submitted a type II variation (NL/H/0819/001/II/003) for the update of a DMF. Together with this update, an additional production site has been introduced and approved.

II.3 Quality

During the MRP, the MAH committed to provide further process validation data of the first 3 full-scale batches. These data have been submitted in February 2010. An AR on the submitted documentation has been sent by the RMS on 15 March 2010 and on 5 April, the final conclusion was drawn that this post-approval commitment is considered fulfilled.
In accordance with the CMD(h) Best Practice Guide on the processing of renewals in the mutual recognition and decentralised procedure (version November 2008) a quality expert statement has been submitted for Quinapril 40 mg confirming:

- That the products are in compliance with the requirements of Directive 2001/83/EC which obliges the MAH Stada Arzneimittel AG to take account of technical and scientific progress and introduce any changes.
- That all changes relating to the quality of the products have been made following applications for variations and that the product conforms to the current CHMP quality guidelines.

The currently authorised specifications for the active substance and the finished products with the qualitative and quantitative composition have been provided.

There are no outstanding quality commitments.

II.4 Clinical Efficacy and Safety

II.4.1 Clinical Efficacy

No new clinical data have become available during the previous period.

II.4.2 Clinical Safety

Summary of Cumulative Experience 22-Sep-2006 to 22-Sep-2009

The MAH submitted within the renewal dossier:

- Periodic Safety Update Report, covering the period 22 September 2006 to 22 September 2009, dated 30 November 2009 and signed.
- Clinical Expert statement, dated 19 February 2010

During the period covered by this report, there were no marketing authorization withdrawals, revocations or suspensions, failures to obtain a marketing authorization renewal, restrictions on distribution, clinical trial suspensions, dosage modifications, changes to target population or indications or formulation changes made for safety reasons.

In October 2007, the Pharmacovigilance Working Party of the CHMP (PhVWP) reviewed available evidence regarding risks associated with the exposure to ACE inhibitors during pregnancy. The PhVWP concluded that data do not unequivocally show that ACE inhibitors are teratogenic if used during the first trimester and that a strict contraindication was not justified. However, women, who plan to become pregnant or are pregnant, should be advised to change antihypertensive treatment to a safer alternative. A contraindication was confirmed for use of ACE inhibitors during the second and third trimester. The MAH suggests to align with the recommendations and agreed text published by the PhVWP during this renewal procedure.

Patient exposure

The MAH provided the estimate on patient exposure, being 5,809 patient years in regular use. The calculation is based on the sales volume of approximately 32,529,840 mg and the assumption of a DDD (Defined Daily Dose) (WHO) of 15 mg.

Adverse events

In the period under review the MAH received a total of 3 case reports concerning quinapril; 1 serious case (adverse events; hyponatraemia and vomiting) and 2 non-serious cases (adverse events sleep disorder, amnesia, confusional state, depression, dizziness, headache, nightmare, visual impairment, balance disorder, and generalised pruritus).

One serious case was identified from literature with the adverse events hypotension, intentional overdose,
and tachycardia.

Studies
No new studies were performed, analysed or targeted in the monitoring period.
No study reports containing important safety findings were published in literature.

Overall safety evaluation
No new information is available on drug interactions, drug abuse or misuse, pregnancy and lactation, special patient groups, or effects of long-term treatment.

II.4.3 Conclusion on Safety
The MAH received a total of 4 case reports in the period under review. The 4 cases contained a total of 15 adverse reactions; 13 non-serious events (3 unlisted) and 2 serious events (0 unlisted).

Quinapril takes part in the PSUR Work Sharing project of the HMA with Denmark acting as P-RMS (DK/H/PSUR/0013). During the assessment, a Core Safety Profile will be established. The MAH committed to submit a type IB variation within 3 months after finalisation of the worksharing procedure to ensure that all safety information listed in the Core Safety Profile is adequately reflected in the SPC and PL Quinapril 40 mg (NL/H/0819/001).

II.5 Product Information

SPC/PIL
The MAH stated that they updated the SPC, PIL and Labelling texts to adapt these texts conform the CMD(h) English QRD Template. Furthermore, the SPC and PIL were adapted conform the “PhVWP Report on ACE inhibitors and Angiotension II Receptor Antagonists and Recommendation on the use during Pregnancy” of October 2007. However, it was noticed by the RMS that the agreed PhVWP text with regard to the use of ACE inhibitors during lactation was not yet included in the SPC and PL. Therefore, the MAH was requested to make some additional changes in the SPC and PL. See paragraph III for the commitment that resulted from this request.

The patient Information Leaflet is harmonised for this product.

Assessment of User Testing
The PL has already been tested (see MRP AR) and therefore, there is no need to provide a user test again.

Labelling
Labelling texts are harmonised for this product.

II.6 Remaining post-approval commitments to be fulfilled by the MAH

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

- The MAH committed to provide further process validation data of the first 3 full-scale batches.
- The MAH committed to submit a type II variation for the procedure SE/H/0392 in order to harmonise this SmPC with the SmPC of the procedure NL/H/0819/01/MR with regard to the indication ‘congestive heart failure’. This type II variation has to be submitted as soon as possible after the finalisation of the MRP, but not later than 3 November 2006.

The MAH has submitted the requested documentation and therefore both post-approval commitments are considered fulfilled (see also above).
III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

In the period covered by this renewal procedure no new important safety issues were identified. The benefit/risk balance of the product remains favourable and therefore the renewal can be granted with unlimited validity, provided that the SPC and PL will be updated as requested (see below). The Common Renewal Date is 31 May 2010.

All issues included in the preliminary assessment report are considered solved. However, there are some outstanding comments with regard to the SPC and PL:

Outstanding RMS comments:
- The MAH is requested to delete the following text at the end of section 4.4:

  “Lactation
  Use of quinapril is not recommended during breastfeeding.”

- The MAH is requested to include the following text, as agreed by the PhVWP, in the SPC and PL:

SPC
Section 4.6:
Lactation:
Limited pharmacokinetic data demonstrate very low concentrations in breast milk (see section 5.2). Although these concentrations seem to be clinically irrelevant, the use of Quinapril in breastfeeding is not recommended for preterm infants and for the first few weeks after delivery, because of the hypothetical risk of cardiovascular and renal effects and because there is not enough clinical experience.
In the case of an older infant, the use of Quinapril in a breast-feeding mother may be considered if this treatment is necessary for the mother and the child is observed for any adverse effect.

Section 5.2 Pharmacokinetic properties
Lactation:
After a single oral dose of 20 mg of quinapril in six breast-feeding women, the M/P (milk to plasma ratio) for quinapril was 0.12. Quinapril was not detected in milk after 4 hours after the dose. Quinalaprilat milk levels were undetectable (<5 µg/L) at all time points. It is estimated that a breastfed infant would receive about 1.6% of the maternal weight-adjusted dosage of quinapril.

PL
Pregnancy and breast feeding
Breastfeeding
Tell your doctor if you are breast-feeding or about to start breast-feeding. Breast-feeding newborn babies (first few weeks after birth), and especially premature babies, is not recommended whilst taking QUINAPRIL.
In the case of an older baby your doctor should advise you on the benefits and risks of taking QUINAPRIL whilst breast-feeding, compared with other treatments.

Commitment (made during this renewal procedure):
The MAH submitted a commitment that a type IB variation for the update SPC and PL for the inclusion of all safety information listed in the Core Safety Profile of Quinapril will be submitted within 3 months after finalisation of the PSUR worksharing procedure DK/H/PSUR/0013

Next PSUR
In July 2009, the MAH agreed to harmonise the PSUR cycle to the EU HBD project of Quinapril. The next PSUR should be submitted within 60 days after the data lock point (DLP) in April 2011 (according to the EU HBD project). Hereafter, the PSUR submission cycle is 3 years. The MAH is requested to submit the next PSUR (also to the P-RMS) within 60 days following the data lock point in April 2011.
The Common Renewal Date is 31 May 2010.
List of abbreviations

ACE      Angiotensin Converting Enzyme
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\text{max} Maximum plasma concentration
CMD(h)   Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV       Coefficient of Variation
DDD      Defined Daily Dose
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
PhVWP    Pharmacovigilance Working Party
PL       Package Leaflet
P-RMS    Periodic Safety Update Report Reference Member State
PSUR     Periodic Safety Update Report
RH       Relative Humidity
SD       Standard Deviation
SPC      Summary of Product Characteristics
t\frac{1}{2}   Half-life
t\text{max}   Time for maximum concentration
TSE      Transmissible Spongiform Encephalopathy
USP      Pharmacopoeia in the United States