CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Fosinoprilnatrium Apotex 10 mg, tablets
Fosinoprilnatrium Apotex 20 mg, tablets
Apotex Europe B.V., the Netherlands

fosinopril (as sodium)

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/1051/001-002/MR
Registration number in the Netherlands: RVG 34873- 34874

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Pharmacotherapeutic group:	ACE inhibitors, plain
ATC code:	C09AA09
Route of administration:	oral
Therapeutic indication:	treatment of hypertension and treatment of symptomatic heart failure.
Prescription status:	prescription only
Date of authorisation in NL:	16 March 2007
Concerned Member States:	Mutual recognition procedure with IT, CZ, PL (withdrawn on 25-8-2009) and UK
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 Fosinoprilnatrium Apotex 10 mg and 20 mg, tablets from Apotex Europe B.V. The date of authorisation was on 16 March 2007 in the Netherlands. The product is indicated for the treatment of hypertension and treatment of symptomatic heart failure.

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

Fosinopril sodium is the ester prodrug of the long-acting ACE inhibitor, fosinoprilat. After oral administration, fosinopril is quickly and fully metabolised to the active fosinoprilat. Fosinopril sodium contains a phosphinic group capable of specific binding to the active site of the peptidyl dipeptidase angiotensin-converting enzyme, preventing the conversion of decapeptide angiotensin I to the octapeptide, angiotensin II. The resulting reduction in angiotensin II levels leads to a reduction in vasoconstriction and a decrease in aldosterone secretion, that might induce a slight increase in serum potassium and a loss of sodium and fluid. Usually, there is no change in renal blood flow or glomerular filtration rate.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator products Newace-10, 10 mg tablets and Newace-20, 20 mg tablets (NL License RVG 15237 and 15238 respectively). The innovator products have been registered in the Netherlands by Bristol-Myers Squibb B.V. since 23 June 1993. In addition, reference is made to Newace 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 applicant has submitted one bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Fozitec 20 mg tablets by Merck Lipha Sante, registered in France. Fozitec is the French name for the innovator product Newace. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. These generic products can be used instead of their reference 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 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 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
Fosinopril is not described in the Ph.Eur.* However, a Ph.Eur. monograph is in development. The drug substance is a white to off-white powder. It is soluble in water and methanol. Fosinopril possesses 4 asymmetric carbon atoms. Optical activity is controlled by a requirement in the specification. Two polymorphs are known (A and B). The polymorph manufactured by the active substance manufacturer (ASM) is Form A.

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/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.

Manufacture
Fosinopril sodium is prepared from two starting materials via a one-step synthesis and subsequent salt forming and purification processes. Adequate certificates of analysis of the starting materials and reagents have been provided. The drug substance has been adequately characterised.

Quality control of drug substance
The drug substance specification is in compliance with the Ph.Eur. monograph "Substances for pharmaceutical use" and with the Ph.Eur. draft monograph, with additional requirements for residual solvents and particle size. The specification is acceptable in view of the route of synthesis and the various ICH guidelines.

Stability of drug substance
Stability data have been obtained during storage at 25°C/60% RH and 40°C/75% RH. The drug substance was adequately stored. The substance is stable at both conditions. Based on the stability data provided, the claimed retest period of 3 years, without special storage conditions, has been granted.

** 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.*

Drug product
The product is formulated as an uncoated, direct-release tablet. The tablets are packaged into Al-Al blisters. Each tablet contains the active ingredient fosinopril sodium. Two strengths are produced: 10 mg and 20 mg.
The 10 mg tablets are white and shaped like a capsule with indents. On one side they are engraved with the letters "APO" and on the other side with "FOS-10".
The 20 mg tablets are white and their shape is oval. On one side they are engraved with the letters "APO" and on the other side with "FOS-20".
The excipients are: anhydrous lactose, crospovidone type A (E1202) and zinc stearate.

Pharmaceutical development

The development of the product is satisfactorily performed and explained. The excipients used are common in the manufacture of tablets and some are also present in the innovator product. The packaging materials are usual and suitable for the product at issue. The objective was to develop a product that would be bioequivalent with the innovator product Newace.

Manufacture of the product
The tablets are prepared from a common granulate. The granulate is compressed. Each tablet strength has different markings and shape. The manufacturing process has sufficiently been described.

Quality control of drug product
The product specification for the tablets includes tests for appearance, identification, assay, water content, degradation products, dissolution rate, related substances, mass, microbiological requirements and uniformity of dosage units. The proposed tests and requirements are acceptable. Batch analysis data have been provided on three pilot batches of each strength. Compliance with the release requirements is demonstrated.

Stability of drug product
The tablets have been stored at 25°C/60% RH, 30°C/65%RH and 40°C/75% RH. A decrease in assay is seen at accelerated conditions. The product is shown to be stable at long term and intermediate conditions. The claimed shelf-life of 24 months (bottles), 21 months (blisters) if stored below 25°C has been granted. The storage conditions are: *"Do not store above 25°C"* and *"Store in the original package in order to protect from moisture"*. The MAH committed to continue the stability study until 36 months have been covered, and to perform In-Use stability to establish a period of time during which a multi dose (i.e. HDPE container) can be used while retaining quality.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.2 Non-clinical aspects

This product is a generic formulation of Newace, 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 fosinopril 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

Fosinopril is a well-known active substance 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 Fosinoprilnatrium Apotex 20 mg is compared with the reference products Fozitec 20 mg (France).

The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Fosinoprilat is the active metabolite of fosinopril and therefore its pharmacokinetic parameters are critical for the assessment of bioequivalence. The choice of the reference products in the bioequivalence studies have been justified by comparison of dissolution results.

Fosinonopril as well as fosinoprilat are absorbed in the proximal duodenum. The presence of food slows down the absorption process but does not influence the extent of bioavailability. 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.

Bioequivalence study
A randomised, open-label, single-dose, cross-over, bioequivalence study was carried out under fasted conditions in 45 healthy volunteers, aged 18-55 years. The subjects were enrolled in two trenches of 33 and 12 subjects four days apart. Each subject received after an overnight fast of at least 10 hours a single dose (20 mg) of one of the 2 fosinopril formulations. The first standard meal was served 4 hours after dosing. For each subject there were 2 dosing periods, separated by a washout period of 7 days. Blood samples were taken predose and at 0.166, 0.33, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48 and 60 hours after administration of the products.

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.

Results
Three subjects were withdrawn from the study, respectively because of a swollen gum that was considered not related to the study medication, voluntary withdrawal and non-compliance. Forty-two subjects completed all study periods and were eligible for pharmacokinetic analysis (table 1). A separate analysis is provided for the 33 subjects initially recruited (table 2).

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

Treatment N=42	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	1829 ± 600	1870 ± 614	230 ± 103	3 (1.5-6)	11.1 ± 7.5
Reference	1806 ± 647	1838 ± 660	227 ± 92	2.5 (1.5-6)	10.2 ± 4.9
***Ratio (90% CI)**	1.02 (0.96-1.08)	1.04 (0.99-1.10)	1.00 (0.94-1.08)	---	---
CV (%)	16	15	19	---	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life
* ln-transformed values

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

Treatment N=33	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	1863 ± 612	1909 ± 629	233 ± 115	---	---
Reference	1892 ± 633	1927 ± 648	239 ± 96	---	---
***Ratio (90% CI)**	1.02 (0.96-1.08)	1.01 (0.94-1.08)	0.95 (0.88-1.03)	---	---
CV (%)	16	15	17	---	---

$AUC_{0-\infty}$ 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} based on data of 42 subjects 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 fosinoprilat under fasted conditions, it can be concluded that test Fosinoprilnatrium Apotex 20 mg tablet and the reference Fozitec 20 mg tablet are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The design of the study resembles an add-on setup that is normally not acceptable for studies that aim to demonstrate bioequivalence. Due to unforeseen reasons only 33 subjects were available in the scheduled period 1 of the study. It was possible to dose the second group (12 subjects) only four days after the first group using the same study conditions. Therefore, the study was analysed by the MAH as a regular two-period study and not as add-on study. In a separate analysis (table 2) of the first group of 33 subjects performed by the assessor, bioequivalence could already be demonstrated for those first 33 subjects. Therefore, the design of the study did not influence the decision on bioequivalence.

Extrapolation of results
The 10 mg tablets are dose proportional with the 20 mg tablets. The pharmacokinetics of the active substance are linear in the dose range 10-20 mg and the in vitro dissolution profiles show rapid dissolution (>80% within 30 minutes). Therefore, the conclusion that the 20 mg Fosinoprilnatrium Apotex 20 mg tablets are bioequivalent can be extrapolated to the 10 mg tablets.

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
Fosinopril was first approved in 1990, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of fosinopril 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 applicant 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

Package leaflet
The MAH committed to improve clarity and make the leaflet more user-friendly by simplifying statements and section lay-outs.

SPC
The content of the SPC approved during the mutual recognition procedure is in accordance with that accepted for the reference product Newace. The MAH committed to update section 4.3 Contra-indications and section 4.6 Pregnancy and lactation according to the final opinion of the CHMP and the recommendations from the Pharmacovigilance Working Party on the use of ACE inhibitors during pregnancy, and change the package leaflet accordingly.

Readability test
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. There were sufficient questions about the critical sections. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The test consisted of two testing rounds with 10 participants each. The results of the first test round indicated that several sections of the package leaflet could be improved, especially to improve the comprehensibility/applicability of the information. The second test round with the adapted text led to a readability score of 89%, i.e. more than 8 out of 10 respondents answered the questions correctly. The conclusions in the report are clear, concise and clearly presented. The readability test is considered acceptable.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Fosinoprilnatrium Apotex 10 mg and 20 mg tablets have a proven chemical-pharmaceutical quality and are generic forms of Newace-10 and Newace-20, respectively. Newace 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 content of the SPC approved during the mutual recognition procedure is in accordance with that accepted for the reference product Newace.

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. Fosinoprilnatrium Apotex 10 mg and 20 mg tablets were authorised in the Netherlands on 16 March 2007.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The mutual recognition procedure was finished on 17 July 2007. The concerned member states, on the basis of the data submitted, considered that bioequivalence has been demonstrated for Fosinoprilnatrium Apotex 10 mg and 20 mg tablets with the reference product, and have therefore granted a marketing authorisation.

A European harmonised birth date has been allocated (3 July 1990) and subsequently the first data lock point for fosinopril is July 2009. The first PSUR will cover the period from July 2007 to July 2009, after which the PSUR submission cycle is 3 years.

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

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

Quality – Drug product
- The MAH commited to perform in-use stability testing to establish a period of time during which a multi dose (i.e. HDPE container) can be used while retaining quality.
- The MAH committed to continue the stability study until 36 months have been covered. The first three full-scale batches of each strength will be placed in the study (an adequate protocol is submitted) when such batches have been made. These batches will also be used in a full-scale validation study.

Product information - PIL
- The MAH committed to improve clarity and make the leaflet more user-friendly by simplifying statements and section lay-outs.

Product information – SPC
- The MAH committed to update section 4.3 Contra-indications and section 4.6 Pregnancy and lactation according to the final opinion of the CHMP and the recommendations from the Pharmacovigilance Working Party on the use of ACE inhibitors during pregnancy, and change the package leaflet accordingly.

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
Submission of an updated DMF version of the active pharmaceutical ingredient.	NL/H/1051 /001-002/ II/001	II	26-9-2008	---	Non Approval	N
Submission of a new DMF.	NL/H/1051 /001-002/ II/002	II	26-9-2008	25-11-2008	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. All other manufacturing operations except batch release.	NL/H/1051 /001-002/ IB/003	IB	22-7-2008	21-8-2008	Approval	N
Minor change in the manufacture of the finished product.	NL/H/1051 /001-002/ IB/004	IB	22-7-2008	21-8-2008	Approval	N
Change in test procedure of the finished product. Other changes to a test procedure, including replacement or addition of a test procedure.	NL/H/1051 /001/002/ IB/005	IB	22-7-2008	21-8-2008	Approval	N
Change in the shelf-life of the finished product. As packaged for sale.	NL/H/1051 /001-002/ IB/006	IB	22-7-2008	21-8-2008	Approval	N
Change in test procedure of the finished product. Minor change to an approved test procedure.	NL/H/1051 /001-002/IA/007	IA	22-7-2008	5-8-2008	Approval	N
Update of SPC section 4.3 Contra-indications and section 4.6 Pregnancy and lactation according to the final opinion of the CHMP and the recommendations from the PhVWP on the use of ACE inhibitors during pregnancy, and to change the package leaflet accordingly.	NL/H/1051 /001-002/ II/008	II	16-3-2009	7-4-2009	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Primary packaging site. Solid pharmaceutical forms, e.g. tablets and capsules.	NL/H/1051 /001-002/ IA/009	IA	13-10-2008	28-10-2008	Approval	N
Change in the name of a manufacturer responsible for batch release and prim. /sec. packaging.	NL/H/1051 /001-002/ IA/010	IA	10-4-2009	24-4-2009	Approval	N
Withdrawal of the marketing authorisation in Poland.	NL/H/1051 /001-002/ MR	Withdrawal	---	25-8-2009	---	N
Renewal of the marketing authorisation.	NL/H/1051 /001-002/ R/001	Renewal	17-12-2009	31-5-2010	Approval	Y, Annex I
• Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non- sterile medicinal products. • Change to batch release arrangements and quality control testing of the finished product. Replacement or addition of a site where batch control/testing takes place.	NL/H/1051 /002/IB/ 011/G	IB/G	12-1-2011	3-2-2011	Approval	N

Annex I - Renewal of the marketing authorisation

I RECOMMENDATION

Based on the review of the data submitted for this renewal application, the RMS is of the opinion that the benefit/risk balance of Fosinoprilnatrium Apotex, NL/H/1051/001-002/R/001, is still positive.
The RMS therefore recommends the renewal of the Marketing Authorisation for Fosinoprilnatrium Apotex.
The RMS is also of the opinion that the renewal can be granted with unlimited validity.

II SCIENTIFIC DISCUSSION

II.1 Introduction

Fosinoprilnatrium Apotex is an angiotensin converting enzyme (ACE) inhibitor indicated in the treatment of mild to moderate essential hypertension in those patients in whom treatment with a diuretic or a β-blocker was found ineffective or has been associated with unacceptable adverse effects. It may be used alone or in association with thiazide diuretics. Fosinoprilnatrium Apotex is also indicated in the management of symptomatic congestive heart failure as adjunctive treatment with diuretics and, where appropriate, digoxin.

The international and the EU harmonised birth date is 03 July 1990. Fosinoprilnatrium Apotex was first registered in Canada on 31 March 2005 and has been registered in the Netherlands since 16 March 2007. The product is licensed through the MR procedure with NL as RMS and the Czech Republic, Italy and United Kingdom as CMS. Overall, the product has been approved and marketed in 7 countries, i.e. Australia, Canada, Czech Republic, Italy, the Netherlands, the United Kingdom and the USA.

Using the worldwide sales data and defined daily dose (DDD) of 15 mg orally, the total number of tablets sold during the period of the report represents a patient exposure of 0.62 million patient years. No studies with Fosinoprilnatrium Apotex have been performed during the period of this report.

RMS's comment:
Fosinopril takes part in the EU Harmonised Birth Dates project of the Heads of Medicines Agencies. The European Harmonised Birth Date has been set on 03 July 1990 with a next allocated data lock point of July 2012. The MAH is requested to submit the next PSUR with a DLP of July 2012.

II.2 Module 1/GMP compliance statements

Manufacturer drug product, packaging, batch control and batch release
The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product within the Community. For these manufacturing sites within the Community, the RMS has 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.

Manufacturer active ingredient
The RMS has accepted the statements from the qualified person of the manufacturer of the tablets/manufacturer responsible for batch release as assurance that acceptable standards of GMP are in place at this site.

Details of the following contact persons have been provided:
• Qualified person in the EEA for pharmacovigilance

• Contact person in the EEA with the overall responsibility for product defects and recalls
• Contact person for scientific service in the EEA in charge of information about the medicinal product

II.3 Quality

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 fosinopril tablets confirming:
- That the products are. in compliance with the requirements of Directive 2001/83/EC which obliges the MAH "…. 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.

Post-approval commitments
The following post-approval commitments regarding quality have been made during the initial mutual recognition procedure:

Quality
1. *To perform In-Use stability for Micro Testing to establish a period of time during which a multi dose (i.e. HDPE container) can be used while retaining quality.*
This commitment is in the process of being fulfilled, as the approved in-use stability protocols have been submitted.

2. *To submit an updated DMF as a post approval variation after the end of the MR procedure.*
This commitment has been fulfilled through variation NL/H/1051/001-002/II/001.

Medicinal product
3. *The stability study will continue until 36 months have been covered.*
This commitment has been fulfilled through variation NL/H/1051/001-002/IB/006. The 36 months stability data on submission batches has been provided as part of this shelf-life extension variation submitted on 11/07/2008 and approved on 21/08/2008.

4.*The first three full-scale batches of each strength will be placed in the study (an adequate protocol is submitted) when such batches have been made.*
This commitment has been fulfilled since the first three full-scale batches of each strength were placed on stability. This stability study is currently on-going and will continue as per the approved protocol. Please see attached a summary table with the batches placed on stability.

5. These batches will also be used in a full-scale validation study.
This commitment fulfillment is currently on-going.

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

II.4.2.1 Summary of Cumulative Experience 20 April 2005 to 31 July 2009

The product has been approved and marketed in 7 countries, i.e. Australia, Canada, Czech Republic, Italy, the Netherlands, the United Kingdom and the USA.
Using the worldwide sales data and defined daily dose (DDD) of 15 mg orally, the total number of tablets sold during the period of the report represents a patient exposure of 0.62 million patient years. No studies with the Fosinoprilnatrium Apotex tablets have been performed during the period of this report.

II.4.2.2 Report of Post Marketing Experience 20 April 2005-31 July 2009
The MAH has submitted a license renewal application through the Mutual Recognition Procedure with the Netherlands acting as Reference Member State.

I. Reviewed period

As part of the license renewal application the MAH submitted the following documents:
- PSUR covering the period 01 August 2006 to 17 August 2006
- PSUR covering the period 18 August 2006 to 17 August 2007
- PSUR covering the period 18 August 2007 to 17 August 2008
- PSUR covering the period 18 August 2008 to 31 July 2009
- A Summary Bridging Report, dated 07 September 2009
- Clinical Expert Statement, dated 24 September 2009, signed by Dr. Colin OWEN d'Cunha,
- The SPC in English with proposed updates in track-changes-modus.

This is the first renewal application for the product.

II. Actions taken for safety reasons

The Pharmacovigilance Working Party (PhVWP) issued the recommendations regarding the use of ACE inhibitors during pregnancy and lactation (Doc. Ref.: CMDh/PhVWP/007/2008; December 2008) and recommendations regarding the use of fosinopril during pregnancy (Doc. Ref.: CMDh/PhVWP/042/2008; March 2009). The MAH has included texts in line with these recommendations in the SPC with variation NL/H/1051/01-02/II/08 (day 90 was 7 April 2009).

In addition, the EU work sharing procedure in the assessment of paediatric data was finalised in July 2008. The MAH has submitted a proposal to update the SPC in line with these recommendations.

RMS's comment:
Texts in line with the PhVWP recommendations regarding the use of ACE inhibitors during pregnancy and lactation are already included in the SPC.
With this renewal application the MAH also submitted a proposal to update the SPC. This proposal includes the wording agreed in the EU work sharing procedure in the assessment of paediatric data was finalised in July 2008.

III. Changes to the Reference safety information

The MAH used Canadian Product Monograph dated 06 February 2008 as Reference Safety Information (RSI).
During the period under review changes were made to three (3) sections in the RSI:
- Warnings
- Precautions
- Information for patients

These changes were accepted, the SPC has been updated in accordance with these changes.

Of note, in the cover letter the MAH announces "*In agreement with the RMS, the European work sharing of paediatric data is implemented during this renewal*." The EU work sharing procedure in the assessment of paediatric data was finalised in July 2008 with an agreed wording. The MAH has implemented paediatric wording in this renewal.

IV. Patient exposure

Using the worldwide sales data and defined daily dose (DDD) of 15 mg orally, the total number of tablets sold during the period of the report represents a patient exposure of 0.62 million patient years. No studies with the Fosinoprilnatrium Apotex, have been performed during the period of this report.

V. Adverse reactions

During the period under review, 6 medically confirmed case reports comprising 11 ADRs were received. Of the presented cases, four (4) cases were regarded serious (three (3) listed, one (1) unlisted). Additionally 4 case reports were received from consumers for which a medical confirmation could not be obtained. There were no reports from clinical trials and no fatal cases.

One serious, unlisted case report was received from a regulatory authority. The case involved a 78-year old female patient who experienced angioedema and swelling of the left side of tongue and the mouth while using fosinopril. The RSI does not list swelling of the mouth, but lists swollen tongue and angioedema associated with the use of fosinopril. The MAH states that swelling of the mouth could occur as a manifestation of angioedema of the face.

Based on the presented cases, no action is required.

VI. Studies

There were no newly analysed company-sponsored studies and no targeted new studies during the reporting period.

VII. Published studies

During the reporting period there were two (2) published safety studies identified in the scientific literature:

Kahegeshe NL., Pestiauk A., Henry JP. and Van Cauter J. Transient recurrent ascites. *Acta Gastroenterologica Belgica.* 2006; 69(4); 381-3.

Kahegeshe NL reported a case of 31-year old woman who was diagnosed with fosinopril induced angiodema of small bowel. The MAH states that angioedema is listed in the CCDS, however it does not mention specifically about small bowel angioedema. The MAH states that the issue will be closely monitored.

Pilote L. Angiotensin-converting enzyme inhibitors in elderly patients with acute myocardial infarction: a class effect? *Cardiology review*. 2006 Dec.
The author performed retrospective cohort study in order to evaluate whether all ACE inhibitors are associated with a similar 1-year mortality rate in patients aged 65 years or older who have had an acute myocardial infarction. Ramipril was used as an a priori reference category and the adjusted hazard ration for fosinopril compared to ramipril was 1.71 (95% CI 1.29 to 2.25). The results showed that patients in the fosinopril group had markedly higher 1-year mortality rates compared with those in the ramipril reference group.
The MAH states that fosinopril is not indicated for use as discussed in the study.

VIII. Efficacy related information, Overdose, Drug Abuse, Special Patient Groups, Effects of Long Term Treatment, Medication Errors

No new safety information has been identified with regard to the above mentioned topics.

IX. Pregnancy and lactation

The Pharmacovigilance Working Party (PhVWP) issued the recommendations regarding the use of ACE inhibitors during pregnancy and lactation. Based on these recommendations changes were made to the CCSI and a new version prepared.

The MAH has updated the SPC in line with the PhVWP recommendations with variation NL/H/1051/01-02/II/08. No further action is required.

X. Late breaking information

After the Data Lock Point (DLP), 31 July 2009, the MAH received one non-serious listed medically confirmed case report related to safety of the use of Fosinopril Apotex.

Based on this case, no action is required.

II.4.3 Conclusion on Safety

Overall, 6 case reports comprising 11 ADRs were received during the period of the PSUR covering the period 01 August 2006 to 31 July 2009. Four (4) cases were regarded as serious. Additionally 4 case reports were received from consumers for which a medical confirmation could not be obtained. One (1) medically confirmed case report was received after DLP (non-serious, listed).
There were no reports from clinical trials and no fatal cases. No new safety issues were identified based on spontaneous reports, literature or published studies.
Fosinopril takes part in the PSUR synchronisation project of the Heads of Medicines Agencies. The next PSUR should cover the period from 01 August 2009 to 31 July 2012 and should be submitted within 60 days from the data lock point. During this assessment the core safety profile (CSP) will be agreed on. The MAH should commit to incorporate this CSP and the conclusions drawn based on the PSUR.

The MAH commits to incorporate the core safety profile and the conclusions drawn based on the PSUR as soon as the new texts are made available by the Heads of Medicines Agencies. This is acceptable.

II.5 Product Information

II.5.1 Summary of Product Characteristics

The MAH proposes to include information on the use in children and adolescents in sections 4.2, , 4.8, 5.1 and 5.2 of the SPC (see annex I). This information has been agreed during the EU work sharing procedure in the assessment of paediatric data.

II.5.2 Package leaflet and user testing

II.5.2.1 Package Leaflet

PL are harmonised for this product. The following change has been proposed by the MAH:

Section 3
“Use in children and adolescents is not recommended.
There is limited clinical trial experience of the use of fosinopril in hypertensive children aged 6 years and above. The optimum dosage has not been determined in children of any age. Appropriate dose strength is not available for children weighting less than 50Kg.”

This is acceptable.

II.5.2.2 Assessment of User Testing

The PL has already been tested before start of the Mutual Recognition Procedure. However, the following commitment was made during the MRP:

PIL
The MAH has committed to improve clarity and make the leaflet more user-friendly by simplifying statements and section lay-outs. If necessary, additional user-testing will be performed to confirm that all the key messages about these tablets are readily identified and understood by the participants.

The company responded by stating that the company which performed the readability testing considered that the results of this testing covered all the needs. Should this response be considered as not sufficient, Apotex is ready to propose a new PIL lay-out and if necessary have this lay-out validated through testing.

This was agreed

II.5.3 Labelling

Labelling texts are harmonised for this product. No changes have been proposed by the MAH.

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

The following post-approval commitments are still outstanding:

Area[1]	Description	Due date[2]
Pharmacovigilance	The next PSUR should be submitted after 3 years	September 2012
Pharmacovigilance	The MAH should commit to implement the core safety profile as established by the P-RMS.	As soon as the core safety profile (CSP) is agreed on

[1]Areas: Quality, Non-clinical, Clinical, Pharmacovigilance
[2]Due date for the follow-up measure or for the first interim report if a precise date cannot be committed to.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Based on the data accumulated during the review period, the benefit/risk ratio for the product remains favourable. There have been no new safety issues identified in the period under review.

The member states have granted a renewal of the marketing authorisation with unlimited validity.

Fosinopril takes part in the PSUR synchronisation project of the Heads of Medicine Agencies with a next data lock point (DLP) of July 2012. The MAH will submit the next PSUR within 60 days following this DLP.