CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Fosinoprilnatrium Aurobindo 10 mg and 20 mg, tablets
Aurobindo Pharma B.V., the Netherlands

fosinopril 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/2353/001-002/MR
Registration number in the Netherlands: RVG 105776-105777

24 November 2011

Pharmacotherapeutic group:	angiotensin converting enzyme (ACE) inhibitors, plain
ATC code:	C09AA09
Route of administration:	oral
Therapeutic indication:	treatment of hypertension; treatment of symptomatic heart failure
Prescription status:	prescription only
Date of first authorisation in NL:	1 July 2010
Concerned Member States:	Mutual recognition procedure with ES, FR, IT, MT, RO 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 Aurobindo 10 mg and 20 mg, tablets, from Aurobindo Pharma B.V. The date of authorisation was on 1 July 2010 in the Netherlands. The product is indicated for 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 fosinoprilaat. 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 product NewAce-10 and NewAce-20, 10 mg and 20 mg tablets (NL License RVG 15237 and 15238) which 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 state (reference product). The innovator product by Bristol-Myers Squibb is marketed in the EU under different brand names, including Fosinorm and Staril.

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 one bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Staril 20 mg tablets, registered in the United Kingdom. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products, and no paediatric development programme has been submitted, as this is not required for generic medicinal products.

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 authorisation.

Active substance
The active substance is fosinopril sodium, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The drug substance is a white or almost white crystalline powder, freely soluble in water, sparingly soluble in anhydrous ethanol and practically insoluble in hexane. Fosinopril sodium has four chiral centers, hence it shows optical isomerism with a specific optical rotation. Only one isomer is present as drug substance. Fosinopril can exist in two polymorphic forms (according to the literature forms A and B, of which form A is stable). Fosinopril sodium used in the formulation 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.

Manufacturing process
The synthesis comprises three steps and has been described in sufficient details. Adequate information has been provided on the starting material, including details on its synthesis. Batch size and yields are indicated.

Quality control of drug substance
The drug substance specification is largely in line with the specifications of the Ph.Eur. monograph. All drug substance specifications are either usual or adequately justified. Batch analysis results for three production scale batches are presented. All results met the set requirements.

Stability of drug substance
Stability data on the active substance have been provided for 3 full-scale batches stored at 25°C/60% RH (36 months) and at 40°C/75% RH (6 months). The stability results showed that no significant changes were observed, justifying the claimed re-test period of 3 years without specific storage condition.

** 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
Fosinoprilnatrium Aurobindo 10 mg and 20 mg tablets contain as active substance 10 mg or 20 mg of fosinopril sodium.

Fosinoprilnatrium Aurobindo 10 mg are white to off-white, flat, capsule-shaped, uncoated tablets, with a scoreline with notched sides on both sides, debossed on one side of the tablet with 'X' and '77 ' on either side of the scoreline, and plain on the other side. The tablets can be divided into two equal halves.
Fosinoprilnatrium Aurobindo 20 mg are white to off white, round, biconvex, uncoated tablets with an "X" on one side and "84" on the other side.

The excipients are: anhydrous lactose, microcrystalline cellulose, crospovidone, sodium stearyl fumarate and povidone (K-30).

The tablets are packed in PVC/PE/PVdC/Aluminium blister packs and HDPE bottles with a polypropylene cap containing silica gel sachet and cotton coil.

The two tablets strengths are fully dose proportional. All excipients and quantities used are commonly used in the manufacturing of immediate release tablets. The components comprising the container closure system are suitable and commonly employed for pharmaceutical solid dosage forms.

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The pharmaceutical development of the product has been adequately performed. A bioequivalence study was performed by comparison of the test product with Staril 20 mg tablets from the UK market. The test product is acceptable.

Assay content and impurity profiles of the test and reference product are considered comparable. Also the dissolution profiles of the test and reference product (20 mg strength) were compared in purified water, and at three pH levels. In all the media, both test and reference product drug release was very rapid, i.e. 90% in 15 minutes, only at the lowest pH was lower. Therefore, the dissolution profiles of the 20 mg test and innovator products may be considered similar.

Dissolution profiles of the two strengths of the test product were compared under the same conditions as described below and similar results were found. In view of this and the fact that both strengths are dose proportional and compressed from the same blend, the results of the bioequivalence study with the 20 mg tablet may be extrapolated to the 10 mg tablet from a chemical-pharmaceutical point of view.

The MAH has submitted results of breakability of the 10 mg strength after storage of 2 years at normal conditions. The results demonstrate compliance with the Ph.Eur. requirements.

Excipients

All excipients comply with the European Pharmacopoeia. Additional specifications and in-house analytical methods have been set, based on vendor specifications and these have been adequately described.

Quality control of drug product

The product specification includes tests for description, identification by IR, thickness, average weight and uniformity of dosage units, related compounds, assay, residual solvent, water, dissolution, microbial contamination and subdivision of tablets (uniformity of mass for split halves for the 10 mg strength). The analytical methods have been adequately described and validated. The stability indicating nature of the analytical methods for assay and related substances has been adequately demonstrated.

Batch analysis results have been provided for the two batches including the test bio-batch. The set specifications for release and shelf-life are acceptable in view of the current stability results and applicable guidelines.

Stability of drug product

Stability data on the product has been provided for 2 batches of each strength, stored at 25°C/60% RH (24 months), and 40°C/75% RH (6 months). Additionally, the MAH provided results of breakability of the 10 mg strength after storage of 2 year at 25°C/60% RH (24 months), and 40°C/75% RH (6 months). The results demonstrate compatibility with the Ph.Eur. requirements.

No significant changes are observed in the photostability studies.

All results complied in the long term- and accelerated studies. Trends observed are: an increase in one specific impurity and a decrease in dissolution and disintegration time, more pronounced at accelerated conditions and in the blister pack. Assay results vary and no clear trend was observed.

The in-use stability does not differ significantly from the stability of the product in the unopened tablet container.

In view of the current stability data, a shelf-life of 24 months is approved. The product does not require any special storage conditions.

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

The product does not contain nor is it derived from specified risk material as defined in the European Union Commission Decision (EC) No 999/2001. All excipients have been declared by their respective suppliers to be without risk of TSE/BSE contamination and corresponding certificates have been included.

II.2 Non-clinical aspects

These products are generic formulations 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 other identical products on the market. The approval of this product will not result in an increase in the total quantity of fosinopril sodium 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 sodium 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 Aurobindo 20 mg (Aurobindo Pharma B.V., NL) is compared with the pharmacokinetic profile of the reference product Staril 20 mg tablets (E.R. Squibb & Sons Ltd, UK).

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states.

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

Study design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 36 healthy male subjects with normal body weight, aged 20-46 years. Each subject received a single dose (20 mg) of one of the 2 fosinopril sodium formulations. The tablet was orally administered with 240 ml water after an overnight fast for at least 11 hours. There were 2 dosing periods, separated by a washout period of 9 days.
Blood samples were collected pre-dose and at 0.33, 0.67, 1.0, 1.335, 1.67, 2.0, 2.33, 2.67, 3.0, 3.5, 4.0, 4, 5, 6, 8, 10, 12, 16, 20, 24, 30, 36 and 48 hours after administration of the products.

Analytical/statistical methods
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.

Fosinopril is a prodrug, which is rapidly hydrolyzed *in vivo* to the pharmacologically active diacid, fosinoprilat. Due to the low dose and the rapid metabolism fosinopril concentrations in plasma are very low and were not reliably measurable because of the lack of sensitive enough analytical methods. Demonstration of bioequivalence based on fosinoprilat is therefore acceptable.

Results
One subject was dropped form the study as he was absent during a study period.

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

Treatment N=35	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/m	**t_{max}** h	**$t_{1/2}$** h
Test	3868 ± 810	3941 ± 818	464 ± 108	3.5 1.67 – 5.0	6.86 ± 1.75
Reference	3897 ± 1028	3971 ± 1035	459 ± 96	4.0 2.0 – 5.0	6.86 ± 1.78
***Ratio (90% CI)**	1.01 0.94 – 1.08	1.00 0.94 – 1.08	1.00 0.93 – 1.08		
CV (%)	17	17	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*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of the active metabolite fosinoprilat under fasted conditions, it can be concluded that Fosinoprilnatrium Aurobindo 20 mg and Staril 20 mg are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Food interaction
Fosinopril sodium may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of fosinopril sodium. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Extrapolation to different strengths
A biowaiver has been granted for the 10 mg strength, as the following conditions are fulfilled:

- the pharmaceutical products are manufactured by the same manufacturer and process,
- the pharmacokinetics has been shown to be linear over the therapeutic range,
- the formulations are dose proportional,
- the dissolution profile should be similar under identical conditions for the additional strengths and the strength of the biobatch.

Therefore, the results of the study with the 20 mg formulation can be extrapolated to the other strength according to conditions in Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, section 5.4.

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 sodium 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 sodium can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are

sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC
The content of the SPC approved during the mutual recognition procedure is harmonised with the agreed text for another fosinopril sodium generic.

Readability test
The package leaflet is harmonised with the approved PIL for another generic fosinopril product. A bridging statement was provided, stating that the parent and daughter PIL contain active ingredients of the same pharmacological class, and all the important key messages for safety are the same in both PILs. Beside the content, also the lay-out of the daughter PIL is identical to the parent PIL, which was tested adequately. This rationale was accepted, so no separate user testing is required.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Fosinoprilnatrium Aurobindo 10 mg and 20 mg, tablets have a proven chemical-pharmaceutical quality and are a generic form of NewAce 10 and 20 mg tablets. 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 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 and are in agreement with other fosinopril containing products.

The Board followed the advice of the assessors. Fosinoprilnatrium Aurobindo 10 mg and 20 mg, tablets were authorised in the Netherlands on 1 July 2010.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Fosinoprilnatrium Aurobindo 10 mg and 20 mg, tablets with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 19 September 2011.

The date for the first renewal will be: November 2015.

There were no post-approval commitments made during the procedure.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached