CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Fosinoprilnatrium/Hydrochloorthiazide Aurobindo 20/12.5 mg, tablets Aurobindo Pharma B.V., the Netherlands

fosinopril sodium/hydrochlorothiazide

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB.
It reflects the scientific conclusion reached by the MEB at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

Registration number in the Netherlands: RVG 105685

24 January 2013

Pharmacotherapeutic group:	ACE inhibitors and diuretics
ATC code:	C09BA09
Route of administration:	oral
Therapeutic indication:	essential hypertension in patients who have inadequately responded to the treatment with fosinopril as monotherapy. The fixed dose may also replace the combination of 20 mg fosinopril sodium and 12.5 mg hydrochlorothiazide in patients who have been stabilised on the individual active substances given in the same proportions as separate medications.
Prescription status:	prescription only
Date of authorisation in NL:	30 September 2011
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board of the Netherlands (MEB) has granted a marketing authorisation for Fosinoprilnatrium/Hydrochloorthiazide Aurobindo 20/12.5 mg, tablets from Aurobindo Pharma B.V. The date of authorisation was on 30 September 2011 in the Netherlands.

The product is indicated for treatment of essential hypertension in patients who have inadequately responded to the treatment with fosinopril as monotherapy.
The fixed dose may also replace the combination of 20 mg fosinopril sodium and 12.5 mg hydrochlorothiazide in patients who have been stabilised on the individual active substances given in the same proportions as separate medications.

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.

Hydrochlorothiazide (HCTZ) is a thiazide diuretic and antihypertensive agent which increases plasma renin activity. HCTZ reduces reabsorption of electrolytes in the distal tubuli of the kidneys and increases excretion of sodium, chloride, potassium, magnesium, bicarbonate and water. Excretion of calcium may be reduced. Concomitant administration of fosinopril and HCTZ causes a greater reduction in blood pressure than either of these substances given as monotherapy.

This national procedure concerns a generic application claiming essential similarity with the innovator product DiurAce® 20/12.5 mg tablets (NL License RVG 19938) which was first registered in the Netherlands by Bristol-Myers Squibb B.V. in 1998 (original product). The authorisation was withdrawn in 2010 for non-safety reasons.

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Fosinorm® 20 mg comp tablets, registered in Germany. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

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

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

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substances
The active substances are fosinopril sodium and hydrochlorothiazide, established active substances described in the European Pharmacopoeia (Ph.Eur.*). Fosinopril sodium is a crystalline powder, freely soluble in water, soluble in anhydrous ethanol; it has four chiral centers, hence it shows optical isomerism with a specific optical rotation. It shows polymorphism (Forms A and B); fosinopril sodium manufactured is Form A.

Fosinopril
The Active Substance Master File (ASMF) procedure is used for fosinopril. 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 were presented. All results meet 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 claim 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.*

Hydrocholorthiazide
The CEP procedure is used for HCTZ. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The MAH apply in-house specifications in addition to Ph. Eur. and CEP requirements. The additionally applied specifications are adequate and acceptable. Batch analysis results have been presented by the CEP-holder on 3 batches and the MAH on 1 batch, with results meeting the set requirements.

Stability of drug substance
The active substance is stable for 36 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Medicinal Product

Composition
Fosinoprilnatrium/Hydrochloorthiazide Aurobindo 20/12.5 mg is a peach coloured, round, biconvex, uncoated tablet debossed with 'C 85' on one side and with a deep score line on the other side.
The tablet can be divided into equal halves.

The tablets are packed in aluminium/aluminium blisters and HDPE containers.

The excipients are: anhydrous lactose, croscarmellose sodium, povidone (K-30), glycerol distearate, sodium lauryl sulphate, ferric oxide yellow, ferric oxide red.

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 carried out comparing the test product with the German reference product Fosinorm 20 mg comp. The reference product used in the bio-equivalence study is fully acceptable, as its composition is identical to that of the NL originator product DiurAce. Comparative dissolution studies in different media - purified water, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer - were carried out on the batches used in the bio-equivalence study. The results obtained indicate that more than 80% of both actives is released within 15 minutes in all the media tested.
Breakability of the tablets in compliance with the Ph.Eur. has been demonstrated.

Manufacturing process
The manufacturing process comprises usual steps of sifting of excipients, dry mixing, wet granulation, drying, pre-lubrication blending, lubrication, and compression. The given batch formulae are in accordance with the product composition. A flow diagram of the manufacturing process is present including listing of in-process controls, and all manufacturing steps are described in sufficient detail. Process validation data on the product has been presented for 2 batches of the smallest batch size, and the process validation is considered to be acceptable. For bigger batch sizes process validation schemes have been submitted; the protocols are considered adequate.

Control of excipients
The two ferric oxide excipients comply with USP-NF, and all other excipients with the Ph. Eur. For 7 excipients additional tests are proposed, based on the vendor specifications; this is acceptable. Batch analysis results have been provided for all excipients.

Quality control of drug product
The product specification includes tests for description, identification, identification of iron oxide, thickness, average weight and uniformity of mass of halved tablets, water, dissolution of the two actives, uniformity of dosage units for the two actives, related substances, assay, residual isopropyl alcohol, and microbial contamination. For water content, assay and related substances, different release and shelf-life specifications are applied. The analytical methods have been adequately described and validated. The stability indicating nature of the analytical method for related substances has been adequately demonstrated. Batch analysis results have been provided for the two batches including the test bio-batch.

Stability of drug product

Stability data on the product has been provided for 2 batches stored at 25°C/60% RH (18 months), 30°C/65% RH (12 months) and 40°C/75% RH (2 months). There are considerable differences between the stability data of alu-alu blister packaging and the HDPE container packs, especially from impurities point of view. Based on the results, the following was accepted: a restricted (real-time) shelf life of 18 months with a restricted storage condition "Store below 30°C".

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
For lactose anhydrous it is stated that the product is manufactured from milk sourced from healthy animals in the same conditions as milk collected for human consumption, and that the calf rennet used in manufacture of lactose is produced in accordance with the applicable EU requirements. For all other excipients it is stated that the source is not from animal origin or that there is otherwise no BSE/TSE risk.

II.2 Non-clinical aspects

This product is a generic formulation of DiurAce, which is available on the European market. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the Board agreed that no further non-clinical studies are required.

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 or hydrochlorothiazide released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Fosinopril and hydrochlorothiazide are well-known active substances with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the Board agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Fosinoprilnatrium/Hydrochloorthiazide Aurobindo 20/12.5 mg (Aurobindo Pharma B.V., NL) is compared with the pharmacokinetic profile of the reference product Fosinorm 20 mg comp tablets (Bristol-Myers Squibb, DE).

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 60 healthy male subjects, aged 18-43 years. Each subject received a single dose (20/12.5 mg) of one of the 2 fosinopril/hydrochlorothiazide formulations. The tablet was orally administered with 240 ml water under fasted conditions). There were 2 dosing periods, separated by a washout period of 8 days.

Blood samples were collected pre-dose and at 0.25, 0.50, 0.75, 1.0, 1.25, 1.50, 1.75, 2.0, 2.25, 2.5, 2.75, 3.0, 3.5; 4.0, 4.5, 5, 6,8, 10, 12, 16 ,24,36 and 48 hours after administration of the products.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable. The blood samples were analysed for HCTZ and fosinoprilat (the active metabolite of fosinopril) which is acceptable. The design of the study is acceptable, the washout and sampling period were long enough, the sampling scheme adequate to estimate the pharmacokinetic parameters

Results

Three subjects dropped out the study; one subject was voluntarily withdrawn from the study in period I due to personal reasons, one subject was absent for period II check in and one subject was withdrawn in period II due to diarrhea before dosing. Fifty-seven subjects were eligible for pharmacokinetic analysis.

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

Treatment N=57	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	4443 ± 1185	4538 ± 1181	540 ± 151	4 (1.75-6)	7.35 ± 1.56
Reference	4402 ± 1191	4492 ± 1197	523 ± 171	3.5 (1.75-8)	7.07 ± 1.58
***Ratio (90% CI)**	1.01 (0.97-1.05)	1.01 (0.97-1.05)	1.04 (0.98-1.10)	-	-
CV (%)	13	12	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*

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

Treatment N=57	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	580 ± 134	611 ± 133	78 ± 18	2.25 (1.25-5.00)	9.75 ± 2.03
Reference	580 ± 147	613 ± 146	81 ± 21	2.25 (0.75-4.50)	9.70 ± 2.27
***Ratio (90% CI)**	1.00 (0.97-1.04)	1.00 (0.96-1.04)	0.97 (0.93-1.02)	-	-
CV (%)	10	11	14	-	-

$AUC_{0-\infty}$ 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 fosinoprilat and HCTZ under fasted conditions, it can be concluded that Fosinoprilnatrium/Hydrochloorthiazide Aurobindo 20/12.5 mg and Fosinorm 20/12.5 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The product may be taken without reference to food intake. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Risk management plan

Fosinopril/HCTZ was first approved in 1998, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of the fosinopril/HCTZ combination can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC

The content of the SPC approved during the national procedure is in accordance with that accepted for the reference product.

Readability test

The package leaflet has not been evaluated via a user consultation study. Reference is made to the successfully user tested PIL for Quinapril/HCTZ Aurobindo. A bridging statement was provided, stating that the parent and daughter PIL contain active ingredients of the same therapeutic group, 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/Hydrochloorthiazide Aurobindo 20/12.5 mg, tablets has a proven chemical-pharmaceutical quality and is a generic form of DiurAce® 20/12.5 mg tablets. DiurAce is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors. The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated with the reference product, and has therefore granted a marketing authorisation. Fosinoprilnatrium/Hydrochloorthiazide Aurobindo 20/12.5 mg, tablets was authorised in the Netherlands on 30 September 2011.

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
HCTZ	Hydrochlorothiazide
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
Transfer of the marketing authorisation.	--	MA transfer	3-11-2011	11-11-2011	Approval	N
Replacement of the existing EDMF for fosinopril sodium drug substance with a new Ph.Eur certificate of suitability.	--	IA	23-7-2012	29-8-2012	Approval	N