CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Alendroninezuur Aurobindo 10 mg and 70 mg, tablets
Aurobindo Pharma B.V., the Netherlands

alendronic acid (as sodium alendronate trihydrate)

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/2292/001-002/MR
Registration number in the Netherlands: RVG 103205 and 103208

1 December 2011

Pharmacotherapeutic group:	Drugs affecting bone structure and mineralization, bisphosphonates
ATC code:	M05BA04
Route of administration:	oral
Therapeutic indication:	treatment of postmenopausal osteoporosis (10 and 70 mg); treatment of osteoporosis in men at increased risk of fracture; prophylaxis of glucocorticoid-induced osteoporosis (10 mg).
Prescription status:	prescription only
Date of first authorisation in NL:	20 July 2010
Concerned Member States:	Mutual recognition procedure with ES, IT, PL, 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 Alendroninezuur Aurobindo 10 mg and 70 mg, tablets, from Aurobindo Pharma B.V. The date of authorisation was on 20 July 2010 in the Netherlands.

The product is indicated for:

- Treatment of postmenopausal osteoporosis. Alendronic acid reduces the risk of vertebral and hip fractures (10 mg and 70 mg).
- Treatment of osteoporosis in men at increased risk of fracture. A reduction in the incidence of vertebral, but not of non-vertebral fractures has been demonstrated (10 mg).
- Prophylaxis of glucocorticoid-induced osteoporosis (10 mg).

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

Alendronic acid is a bisphosphonate that inhibits osteoclastic bone resorption with no direct effect on bone formation. Preclinical studies have shown preferential localisation of alendronic acid to sites of active resorption. Activity of osteoclasts is inhibited, but recruitment or attachment of osteoclasts is not affected. The bone formed during treatment with alendronic acid is of normal quality.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator products Fosamax 10 and 70 mg. Fosamax 70 mg tablets has been registered in the United Kingdom since 28 July 1995 by Merck Sharp & Dohme Limited. In the Netherlands, Fosamax 10 mg (NL license RVG 18021) has been registered nationally since 1 April 1996 and Fosamax 70 mg (NL license RVG 26202) has been registered since 21 May 2001 through procedure UK/H/0423/001. In addition, reference is made to Fosamax 10 mg and 70 mg 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 MAH has submitted one bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Fosamax 70 mg tablets, registered in France. 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 substance
The active substance is alendronic acid (as sodium alendronate trihydrate), an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The substance is a white to almost white crystalline powder. It is soluble in water and practically insoluble in methanol and methylene chloride. There is no potential for isomerism in the active substance.

The CEP procedure is used for the active substance. 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 suitablity 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 new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia, the official handbook in which methods of analysis with specifications for substances are laid down by the authorities of the EU.

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

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur. and the additional requirements as mentioned on the CEP. Furthermore, an additional requirement for particle size is included. The specification is acceptable in view of the route of synthesis and the various European guidelines.
Batch analytical data demonstrating compliance with the drug substance specification have been provided for three commercial scale batches.

Stability of drug substance
Stability data on the active substance have been provided for three commercial scaled batches stored at 30°C/65%RH (24 of months) and 40°C/75%RH (6 months). On the basis of the submitted data a re-test period of 2 years without additional storage conditions could be granted. The drug substance has been show to be stable towards the influence of light.

* *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
Alendroninezuur Aurobindo 10 mg and 70 mg contain as active substance 10 mg and 70 mg of alendronic acid (as sodium alendronate trihydrate) respectively. The 10 mg tablets are white to off-white, round, biconvex, uncoated, debossed with ‘F’ on one side and ‘18’ on the other side. The 70 mg tablets are white to off-white, oval, biconvex uncoated, debossed with ‘F’ on one side and ‘21’ on the other side.

The tablets are packed in clear PVC/Aclar - Aluminium foil blister packs. In addition the 10 mg strength is also packed in white opaque HDPE tablet containers with a white opaque polypropylene closure.

The excipients are: microcrystalline cellulose, maize starch, sodium starch glycolate (type A), povidone (kollidon 30) and magnesium stearate.

The composition of both tablet strengths is fully dose proportional. All excipients used and their quantities are common in immediate release tablets and no specific issues with respect to safety are thus expected. The packaging is usual for this type of dosage form.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The objective of the development of the tablets was to obtain optimal flow characteristics and optimal tabletting results whilst maintaining a homogeneous mixture. The batch used in the bioequivalence study was manufactured according to the finalised procedure and with the intended commercial composition. The pharmaceutical development of the product has been adequately performed. A justification for the choice of the French reference product, compared to the Dutch reference product and the related dissolution data of the Dutch reference products, has been submitted. Fast dissolution is observed (more than 85% within 15 minutes).

Manufacturing process
The tablet will be manufactured by means of a wet granulation process. The manufacturing process has been adequately described including mixing times, temperatures, speeds and sieve sizes.
The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for two pilot scale batches of each strength. The product is manufactured using conventional manufacturing techniques. Process validation for full scale batches will be performed post marketing authorization.

Excipients
The excipients comply with the Ph.Eur. specifications, where for several excipients additional in-house specifications (e.g. particle size) have been included. The proposed specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identity, average weight, tablet thickness, dissolution, assay, related substances, uniformity of dosage units, isopropyl alcohol, and microbiological quality. The release and shelf-life requirements/limits are identical, and are acceptable.
The analytical methods for assay, dissolution, related substances, isopropyl alcohol and microbial contamination, have been adequately described and validated. Batch analytical data from the proposed production site have been provided on 2 pilot scale batches of each strength, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for two pilot scaled batches of each strength. The batches were stored at 25°C/60%RH for 24 months and at 40°C/75%RH for 6 months. The conditions used in the stability studies are in accordance with the ICH stability guidelines. The batches were stored in clear PVC-Aclar/Al blisers and for the 10 mg in the smallest and largest HDPE container. Furthermore the tablets were stored in a bulk package. No changes are observed under both storage conditions for all parameters, except for dissolution rate. This is attributed to the used paddle method, the basket method is used in further testing. The tablets were shown to be stable under influence of light. On the basis of the submitted data a shelf-life of 24 months (without additional storage conditions) could be granted for the 10 mg and 70mg tablets. An in-use study for the tablets in the HDPE containers has been included; stability of the product in the container is shown.
Accelerated stability studies and long-term stability studies will be carried out on the first commercial batch for each strength and the first three commercial batches of the maximum batch size for each strength. Testing will be carried out as per stability programme. Long-term stability studies will be conducted on a minimum of one marketed production batch per year. Testing will be carried out as per long-term stability programme. The stability studies will be continued up to the proposed shelf life of the finished product.

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

Good Laboratory Practice
This product is a generic formulation of Fosamax 10 mg and 70 mg, which are 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 alendronic acid 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

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

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Alendroninezuur Aurobindo 70 mg (Aurobindo Pharma B.V, the Netherlands) is compared with the pharmacokinetic profile of the reference product Fosamax 70 mg (MSD, France).

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 150 healthy male (128) and female (22) subjects with normal body mass, aged 18-35 years. Each subject received a single dose (70 mg) of one of the 2 alendronic acid formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. Food was not allowed till 4 hours upon dosing. Subjects were dosed while in sitting posture and were instructed to remain seated or ambulatory for first two hours following the drug administration.There were 2 dosing periods, separated by a washout period of 19 days.
Urine samples were collected at pre dose (-2.0 to 0.0) and at (0.0 to 0.5), (0.5 to 1.0), (1.0 to 2.0), (2.0 to 3.0), (3.0 to 4.0), (4.0 to 6.0), (6.0 to 8.0), (8.0 to 10.0), (10.0 to 12.0), (12.0 to 24.0), and (24.0 to 36.0) hours post dose.

Justification for using urine data
Due to the extremely low plasma concentrations of alendronate, many pharmacokinetic studies rely on determining alendronate concentrations in urine rather than plasma. In the past these studies have been accepted for several generic applications by the Netherlands and other regulatory authorities. Although alendronate can be measured in plasma, the urinary data are still acceptable as urinary excretion is the predominant route of elimination of alendronate and there is no evidence of biotransformation of alendronate. Furthermore the bioavailablitity of alendronate is low and the distribution into the bone is fast. Therefore it is considered acceptable to use urinary excretion data for demonstration of bioequivalence for this bisphosphonate.

Food interaction
Alendronic acid must be taken at least 30 minutes before the first food, beverage or medicinal product of the day with plain water only. Other beverages (including mineral water), food and some medicinal products are likely to reduce the absorption of alendronate. 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.

Analytical/statistical methods
Urine samples were analysed for alendronic acid using a HPLC-FLD method. The analytical method has been adequately validated and is considered acceptable for analysis of the urine samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
In total 137 subjects completed both periods. 3 Subjects were withdrawn due to vomiting within 2 hours after dosing and the other subjects did not show up at different time points of the study. All withdrawals were reported. All individual concentrations are reported.

Safety
Fifty-two adverse events were reported during the study. Most of the complaints were body pain, vomiting, fever or diarrhoea and were resolved before the end of the study.

Table 1. Alendronic acid cumulative urinary excretion in 36 hours (Ae_{0-36h}), maximum urinary excretion rate (R_{max}) and t_{max} (mean, range) for test and references is shown in the table below as mean ± SD.

Treatment N=137	**Ae_{0-36h}** µg	**R_{max}** µg.h	**t_{max}** h
Test	410 ± 218	156 ± 90.5	1.5 ± 0.6
Reference	417 ± 256	150 ± 92.0	1.5 ± 0.5
***Ratio (90% CI)**	1.00 (0.92 – 1.09)	1.04 (0.95 – 1.13)	---
CV (%)	43	46	---

Ae_{0-36h} cumulative amount of alendronate excreted from time zero to 36 hours
R_{max} maximum urinary excretion rate
t_{max} time for maximum concentration

**ln-transformed values*

The 90% confidence intervals calculated for Ae_{0-36} and R_{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 alendronic acid under fasted conditions, it can be concluded that Alendroninezuur Aurobindo 70 mg and Fosamax 70 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

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 qualitative composition of the different strengths is the same,
- the ratio between amounts of active substance and excipients is the same,
- 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 70 mg formulation can be extrapolated to 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

Alendronic acid was first approved in 1993, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of alendronic acid 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 in accordance with the SPC of the innovator Fosamax (UK/H/423/001).

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. The test consisted of a pilot test with 3 participants, followed by two rounds with 10 participants each. There were sufficient questions about the critical sections. The conclusions are clear, concise and clearly presented.The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Alendroninezuur Aurobindo 10 mg and 70 mg, tablets have a proven chemical-pharmaceutical quality and are generic forms of Fosamax 10 mg and 70 mg tablets. Fosamax 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 the product information of the innovator product.

The Board followed the advice of the assessors. Alendroninezuur Aurobindo 10 mg and 70 mg, tablets was authorised in the Netherlands on 20 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 Alendroninezuur Aurobindo 10 mg and 70 mg, tablets with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 23 August 2011.

The date for the first renewal will be: September 2014.

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

Quality - medicinal product

- The MAH committed to provide the Certificate of analysis of the first three commercial batches of each strength of Alendroninezuur Aurobindo tablets as soon as available.
- Accelerated stability studies and long-term stability studies will be carried out on the first commercial batch for each strength and the first three commercial batches of the maximum batch size for each strength. Testing will be carried out as per stability programme.
- Long-term stability studies will be conducted on a minimum of one marketed production batch per year. Testing will be carried out as per long-term stability programme.
- The stability studies will be continued upto the proposed shelf life of the finished product.

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