COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Alendroninezuur Heumann once weekly 70 mg, tablets

(alendronate sodium)

NL/H/4911/001/DC

Date: 25 February 2021

This module reflects the scientific discussion for the approval of Alendroninezuur Heumann . The procedure was finalised on 10 December 2020. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Alendroninezuur Heumann 70 mg once weekly, tablets from Heumann Pharma GmbH.

Alendroninezuur Heumann is indicated for treatment of postmenopausal osteoporosis. It reduces the risk of vertebral and hip fractures.

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Fosamax 70 mg tablets, which has been registered in Germany by MSD Sharp & Dohme GMBH since 29 June 2001.

The concerned member state (CMS) involved in this procedure was Germany.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Alendroninezuur Heumann once weekly 70 mg is a white to off white, oval, biconvex tablet, debossed with “AHI” on one side and plain on other side. Each tablet contains 70 mg alendronic acid (as alendronate sodium).

The tablets are packed in OPA-Al-PVC/Al blister packs

The excipients are: lactose anhydrous, cellulose microcrystalline (E460), croscarmellose sodium, magnesium stearate.

II.2 Drug Substance

The active substance is sodium alendronate trihydrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white crystalline powder, soluble in water, practically insoluble in methanol and in methylene chloride. It has a mono-crystalline structure.

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 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 Ph.Eur.

Manufacturing process

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

Quality control of drug substance

The specification is in line with the Ph.Eur. monograph and the additional requirements from the CEP. Additional tests for particle size, heavy metals, density and microbiological purity are included in the drug substance specification of the MAH.

Batch analytical data demonstrating compliance with the specification have been provided for five batches.

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.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies performed were formulation studies. The excipients are well known and the choices of the packaging and manufacturing process have been justified.

A bioequivalence study was performed with the 70 mg drug product. The batch used in the bioequivalence studies has the same composition and are manufactured in the same way as the future commercial batches. As per NfG on the investigation of bioequivalence, CPMP/EWP/QWP/1401/98 Rev.1/Corr, possibility of carrying out comparative dissolution studies between reference product i.e. Fosamax tablets 10 mg and Alendroninezuur Heumann tablets 10 mg was explored but due to non-availability of the reference sample comparative study was not possible.

As additional testing, the comparative testing of 1 tablet of 70 mg generic tablet and 7x10 tablets of 10 mg generic tablet has been proposed. In this situation, the release profile for both strength is similar and the f2 value is 72.

The approach to compare 1x70 mg versus 7x10 mg tablets is considered acceptable. In view of the fact that no tablets of the 70 mg test bio-batch are available, it is acceptable to use another 70 mg batch. There are now for each test modality clearly at least 2 test points with dissolution results below 85%. In view of the low RSDs the calculated F2 value of 72 is considered reliable. The comparative dissolution testing is considered acceptable.

Manufacturing process

The tablets are manufactured by a direct compression process (sifting, dry mixing, lubrication and compression). The manufacturing process has been adequately validated according to relevant European guidelines. Process validation reports are provided for three batches of the common blend and for three batches of the tablets. As the process is a standard process, the process has been adequately validated.

Control of excipients

All the excipients used in the manufacturing of the tablets are described in Ph. Eur. The specifications are acceptable.

Quality control of drug product

The product specification of the tablets includes tests for description, identification, average weight of the tablets, disintegration time, resistance to crushing, loss on drying, dissolution, uniformity of dosage units, assay, related substances and microbial examination. The release and shelf life limits are identical except for resistance to crushing, loss on drying and related substances. The proposed specification is acceptable. The analytical methods have been adequately described and validated.

Batch analytical data have been provided on five batches, demonstrating compliance with the release specification.

The MAH provided a risk evaluation for the presence of nitrosamine impurities in the Alendroninezuur Heumann tablets. It is concluded that the risk evaluation is sufficiently meeting the requirements as described in Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products.

Stability of drug product

Stability data on the product has been provided on five full-scale batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in OPA-Al-PVC/Al blister.

The tablets are within specification limits for all parameters after 36 months of long term storage and 6 months of storage at accelerated conditions. No changes or trends are observed.

Based on the stability data provided the proposed shelf life of 36 months has been granted with storage condition 'This medicinal product does not require any special temperature storage conditions'.

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.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Alendroninezuur Heumann has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Alendroninezuur Heumann is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Fosamax, which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. 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 member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Alendronate sodium is a well-known active substance 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 member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Alendroninezuur Heumann once weekly 70 mg (Heumann Pharma GmbH, Germany) is compared with the pharmacokinetic profile of the reference product Fosamax 70 mg tablets (Merck Sharp & Dohme, UK).

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

Bioequivalence studies

Design

A single-dose, randomised, four-period, two-treatment, two-sequence, fully replicate crossover bioequivalence study was carried out under fasted conditions in 48 healthy male subjects, aged 18-45 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 10 hours. There were 4 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at at 0.17, 0.33, 0.50, 0.67, 0.83, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 3.50, 4.00, 5.00, 6.00, 7.00, 8.00, 10.00, 12.00, 16.00, 24.00 and 36.00 hours after administration of the products.

The design of the study is acceptable, the wash-out long enough, sampling period long enough, and sampling scheme adequate to estimate pharmacokinetic parameters. 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

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.

Results

Three subjects were withdrawn from the study on medical grounds in Period-I, Period-II and Period-III. Two subjects discontinued from the study on their own accord in Period-II and Period-III respectively. One subject was withdrawn from the study on the grounds of protocol noncompliance in Period-IV. Forty-two subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of alendronic acid 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	137.462 ± 103.7912	149.523 ± 111.0066	41.993 ± 35.6910	1.25 (0.50-2.03)	--
Reference	121.394 ± 85.3216	132.306 ± 91.5026	37.154 ± 27.9706	1.00 (0.50-2.52)	--
***Ratio (90% CI)**	1.09 (0.97-1.22)	1.09 (0.97-1.22)	1.08 (0.96-1.21)	--	--

CV (%)	39.7	39.7	41.2	--	--

$AUC_{0-\infty}$	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
CV	coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Alendroninezuur Heumann once weekly 70 mg is considered bioequivalent with Fosamax 70 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).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Alendroninezuur Heumann.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Fosamax. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report. The MAH claims the submitted PL is identical to the reference product's PL, which has been in use since 2001 and has been updated consequentially. The PIL complies with the QRD-template and the EU requirements for patient leaflets. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Alendroninezuur Heumann 70 mg once weekly, tablets has a proven chemical-pharmaceutical quality and are generic forms of Fosamax 70 mg. 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 Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Alendroninezuur Heumann with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 10 December 2020.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/Justification for refuse