COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Alendroninezuur/Cholecalciferol 1A Pharma 70 mg/2800 IU and 70 mg/5600 IU, tablets (alendronate sodium trihydrate and cholecalciferol)

NL/H/5455/001-002/DC

Date: 21 February 2024

This module reflects the scientific discussion for the approval of Alendroninezuur/Cholecalciferol 1A Pharma 70 mg/2800 IU and 70 mg/5600 IU tablets. The procedure was finalised on 8 February 2023. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
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
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
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
RMS	Reference Member State
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/Cholecalciferol 1A Pharma 70 mg/2800 IU and 70 mg/5600 IU tablets from 1 A Pharma GmbH.

The product is indicated for: the treatment of postmenopausal osteoporosis in women at risk of vitamin D insufficiency. It reduces the risk of vertebral and hip fractures.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Fosavance 70 mg/2800 IU and 70 mg/5600 IU tablets which has been registered in the EEA via a centralised procedure (EU/1/05/310).

The concerned member states (CMS) involved in this procedure were Germany, Ireland, Italy, and Portugal.

II. QUALITY ASPECTS

II.1 Introduction

Alendroninezuur/Cholecalciferol 1A Pharma 70 mg/2800 IU and 70 mg/5600 IU are tablets. The 70 mg/2800 IU strength contains 70 mg of alendronic acid (as sodium trihydrate) and 70 microgram (2800 IU) cholecalciferol. The 70 mg/5600 IU strength contains 70 mg of alendronic acid (as sodium trihydrate) and 140 microgram (5 600 IU) cholecalciferol. The two strengths can be distinguished by the different size, shape, colour and debossing of the tablets:

The Alendroninezuur/Cholecalciferol 1A Pharma 70 mg/2800 IU is an oblong-shaped tablet, white to off-white, biconvex, mottled, engraved with ‘2800’ on one side, 12.3 mm in length and 6.5 mm in width.

The Alendroninezuur/Cholecalciferol 1A Pharma 70 mg/5600 IU is a modified rectangle-shaped tablet, white to off-white tablet, mottled, engraved with ‘5600’ on one side, 11.4 mm in length and 7.2 mm in width.

The excipients are: lactose, microcrystalline cellulose (E460), croscarmellose sodium (E468), magnesium stearate (E572), refined sunflower oil, butylhydroxytoluene (E 321), gelatine, sucrose, maize starch, aluminium magnesium silicate.

The tablets are packed in orientated polyamide/aluminium/polyvinyl chloride//aluminium (oPA/Alu/PVC//Alu) blisters, in cartons.

II.2 Drug Substance

Alendronate sodium trihydrate
One active substance is alendronate sodium trihydrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Alendronate sodium trihydrate is a white or almost white crystalline powder, soluble in water and insoluble in methylene chloride and in methanol. Particle size is not an important aspect since alendronate sodium is freely soluble in water.

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 active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
The active substance is stable for 3 years when stored under the stated conditions. Assessment thereof was part of granting the CEP (and has been granted by the EDQM). The packaging and proposed re-test of 3 years are in line with the CEP.

Cholecalciferol concentrate powder
One active substance is cholecalciferol concentrate powder, an established active substance described in the European Pharmacopoeia (Ph.Eur.). A concentrate powder is deemed acceptable for use because pure cholecalciferol is complicated to handle.

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
Cholecalciferol concentrate powder is obtained by dispersing the active ingredient Cholecalciferol (EP grade) in an appropriate matrix of suitable quality. The manufacturing process consists of dissolving, emulsifying, and utilizing a spraying/encapsulating/drying process. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised, and the manufacturing process is described in sufficient detail.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
Stability data on the active substance have been provided for six batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 24 months. Based on the data submitted, a re-test period could be granted of 18 months when stored below 30°C.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form, and its development is adequately described in accordance with the relevant European guidelines. The two strengths of the fixed dose combination tablet contain next to the two active substances, excipients that are part of the concentrate powder and the tablet excipients.

Manufacturing process
The manufacturing process has adequately been described. In view of the very low dose, the manufacturing process concerns a non-standard manufacturing process. Full scale validation results have been provided for both strengths.

The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three batches of each strength in accordance with the relevant European guidelines.

Control of excipients
The excipients used are well-known. The specifications are according to the corresponding monographs of the current European Pharmacopoeia. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, average mass, mass uniformity, loss on drying, hardness, disintegration, friability, identification and assay of both active substance and butylhydroxytoluene (BHT), related substances-, dissolution- and uniformity of content of both active substances, and microbial contamination. Limits in the specification

have been justified and are considered appropriate for adequate quality control of the product. Appropriate tests for nitrosamine presence are performed on the final product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data three batches of each strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided from six batches (three of each strength) stored at 25°C/60% RH (12 months) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. Photostability studies as per ICH guidelines have been performed. It was concluded that the product is not affected by UVA light and daylight in the proposed packaging. On basis of the data submitted, a shelf-life was granted of 24 months. No specific storage conditions needed to be included in the SmPC or on the label.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM for cholecalciferol and lactose 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.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Alendroninezuur/Cholecalciferol 1A Pharma 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/Cholecalciferol 1A Pharma is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Fosavance which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided,

which was 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 trihydrate and cholecalciferol concentrate powder are well-known active substances with established efficacy and tolerability. Clinical overviews have been provided, which is based on scientific literature. The member states agreed that no further clinical studies are required, besides the two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Alendroninezuur/Cholecalciferol 1A Pharma 70 mg/2800 IU and 70 mg/5600 IU tablets (Sandoz B.V., Netherlands) was compared with the pharmacokinetic profile of the reference product FosavanceE 70 mg/2,800 IU and 70 mg/5,600 IU tablets from intro (N.V. Organon, Netherlands).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition. The tested media were water, acid pH 1.2, acetate buffer pH 4.5, and phosphate buffer pH 6.8. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing. For alendronic acid, all products showed more than 85% dissolution after 15 minutes in all media. For cholecalciferol, the profiles are also similar with QC method (more than 85% in 15 minutes) but in the other media the dissolution of the reference product Fosavance was much higher than for the proposed product. The company indicates that according to EMEA Dissolution Guideline, in the event that the results of comparative *in vitro* dissolution of the biobatches do not reflect bioequivalence as demonstrated *in vivo* the latter prevails.

Bioequivalence studies

Study 1 - 70 mg/2800 IU tablets under fasting conditions

Design

A single-dose, randomised, four-period, two-treatment, two-sequence, crossover open label bioequivalence study was carried out under fasted conditions in 47 male subjects, aged 20-44 years. Each subject received a single dose (70 mg/2800 IU) of one of the two active substance formulations. The tablet was orally administered with 240 mL water after an overnight fast of at least 10 hours. There were four dosing periods, separated by a washout period of 14 days.

Blood samples for alendronate were collected pre-dose and at 0.167, 0.333, 0.5, 0.667, 0.833, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 10, 12, 16 and 24 hours after administration of the products.

Blood samples for cholecalciferol were collected pre-dose and at 2, 4, 6, 8, 9, 10, 11, 12, 14, 16, 18, 24, 36, 48, 72 and 96 hours after administration of the products.

The design of the study is acceptable.

The administration recommendation of Alendroninezuur/Cholecalciferol 1A Pharma is that it must be taken with water only (not mineral water) at least 30 minutes before the first food, beverage, or medicinal product (including antacids, calcium supplements and vitamins) of the day. It is likely that food and beverages (including mineral water), calcium supplements, antacids, and some oral medicinal products will interfere with absorption of alendronate acid. Therefore, the drug is instructed to be taken under fasting conditions.

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
59 subjects were planned for inclusion in the study. Nine subjects withdrew of their own accord at the start of the study, and one subject was excluded. 49 subjects were enrolled in the study. Two subjects withdrew before period I. During period I, one subject withdrew due to adverse events (emesis). Before period II, one subjects was discontinued due to non-compliance of the study protocol. At period II, another subject withdrew of their own accord. Before period III, one subject withdrew of their own accord. 47 subjects were available for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of alendronate acid, 70 mg under fasted conditions.

Treatment N= 44-45	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test (administration 1)	102.39 ± 62.61	108.67 ± 65.68	33.46 ± 21.01	1.25 (0.50 - 2.00)
Test (administration 2)	148.20 ± 123.01	158.90 ± 129.79	46.29 ± 34.12	1.0 (0.5- 2.0)
Reference (administration 1)	107.72 ± 87.20	114.21 ± 90.46	33.25 ± 25.35	1.0 (0.5- 2.0)
Reference (administration 2)	145.56 ± 86.99	156.32 ± 91.88	46.86 ± 28.24	1.0 (0.5 - 2.0)
***Ratio (90% CI)**	0.96 (0.87 – 1.06)	0.96 (0.87 – 1.06)	0.97 (0.87 – 1.08)	-

$AUC_{0-\infty}$	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 = 24 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of cholecalciferol, 2800 UI mg under fasted conditions.

Treatment N= 41-45	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	C_{max} (ng/mL)	t_{max} (h)
Test (administration 1)	116.40 ± 44.86	135.55± 48.34	4.19 ± 1.18	10.0 (8.0 - 16.0)
Test (administration 2)	124.75 ± 35.98	144.22 ± 35.15	4.17 ± 0.93	12.0 (8.0 - 24.0)
Reference (administration 1)	117.79 ± 49.32	138.20 ± 49.06	4.29 ± 1.29	10.0 (8.0 - 16.0)
Reference (administration 2)	127.28 ± 40.34	147.27 ± 41.21	4.29 ± 1.14	12.0 (8.0 - 16.0)
***Ratio (90% CI)**	1.02 (0.94 – 1.10)	1.01 (0.94 – 1.08)	1.00 (0.94 – 1.05)	-

$AUC_{0-\infty}$	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 = 72 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Study 2 - 70 mg/5600 IU tablets under fasting conditions

Design

A single-dose, randomised, four-period, two-treatment, two-sequence, crossover open label bioequivalence study was carried out under fasted conditions in 69 healthy male (51) and female (18) subjects, aged 18-45 years. Each subject received a single dose (70 mg/2800 IU) of one of the two active substance formulations. The tablet was orally administered with 240 mL water after an overnight fast of at least 10 hours. There were four dosing periods, separated by a washout period of 14 days.

Blood samples for alendronate acid were collected pre-dose and at 0.167, 0.333, 0.5, 0.667, 0.833, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 10, 12, 16 and 24 hours after administration of the products.

Blood samples for cholecalciferol were collected pre-dose and at 2, 4, 6, 8, 9, 10, 11., 12, 14, 16, 18, 24, 36, 48, 72 and 96hours after administration of the products.

The design of the study is acceptable.

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

74 subjects were planned for inclusion in the study. One subject failed to check in before period I. Four subjects withdrew before period I of their own accord. 69 subjects were enrolled in the study. During period 1, four subjects subject withdrew due to adverse events (fever with chills and rigor, chest pain). One subject withdrew of their own accord. During period 2, two subjects withdrew due to adverse events (pyrexia, and pyrexia and dizziness). Four subjects withdrew of their own accord. During period 3, one subjects withdrew due to adverse events (menorrhagia) and one subject withdrew of their own accord. 55 subjects were eligible for pharmacokinetic analysis.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of alendronate acid, 70 mg under fasted conditions.

Treatment N= 55	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	146.10 ± 77.47	155.35 ± 81.49	46.43 ± 24.38	1.0 (0.5 - 3.0)
Reference	144.15 ± 69.00	154.19 ± 73.03	46.84 ± 24.07	1.0 (0.5 - 3.0)
***Ratio (90% CI)**	1.01 (0.93 – 1.09)	1.00 (0.92 – 1.09)	1.01 (0.92 – 1.09)	-

$AUC_{0-\infty}$	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 = 24 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of cholecalciferol, 5600 UI mg under fasted conditions.

Treatment N=55	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	455.93 ± 142.97	487.66 ± 154.63	12.78 ± 3.99	12.0 (8.0 - 18.0)
Reference	475.93 ± 133.65	510.52 ± 147.34	13.13 ± 3.41	12.0 (8.0 - 18.0)
***Ratio (90% CI)**	0.95 (0.91 – 0.99)	0.94 (0.91 – 0.98)	0.96 (0.92 – 0.99)	-

$AUC_{0-\infty}$	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 t = 96 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Conclusion on bioequivalence studies:
The 90% confidence intervals calculated in studies 1 and 2 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 studies Alendroninezuur/Cholecalciferol 1A Pharma 70 mg/2800 IU and 70 mg/5600 IU is considered bioequivalent with Fosavance 70 mg/2800 IU and 70 mg/5600 IU.

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/Cholecalciferol 1A Pharma 70 mg/2800 IU and 70 mg/5600 IU.

Table 5. Summary table of safety concerns as approved in RMP

Important identified risks	Osteonecrosis of the jaw Oesophageal adverse experience
Important potential risks	Atypical femoral fracture
Missing information	Use during pregnancy and lactation fossa Use in patients below 18 years of age Use in patients with severe renal insufficiency [GFR less than 35 mL/min]

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 Fosavance. No new clinical studies were conducted. The MAH demonstrated through two bioequivalence studies 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

The package leaflet (PL) 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.

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Alendronic acid/Cholecalciferol 70 mg/

5600 IU, NL/H/3587. The bridging report submitted by the MAH has been found acceptable; bridging is justified for readability of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Alendroninezuur/Cholecalciferol 1A Pharma 70 mg/2800 IU and 70 mg/5600 IU tablets have a proven chemical-pharmaceutical quality and are generic forms of Fosavance 70 mg/2800 IU and 70 mg/5600 IU tablets. Fosavance 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/Cholecalciferol 1A Pharma 70 mg/2800 IU and 70 mg/5600 IU with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 8 February 2023.

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
-	-	-	-	-	-