Public Assessment Report

Scientific discussion

Alendroninezuur/Cholecalciferol Sandoz 70 mg/5600 IU, tablets

(sodium alendronate trihydrate/cholecalciferol)

NL/H/3578/001/DC

Date: 16 November 2017

This module reflects the scientific discussion for the approval of Alendroninezuur/Cholecalciferol Sandoz 70 mg/5600 IU, tablets. The procedure was finalised on 22 June 2016. 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
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/Cholecalciferol Sandoz 70 mg/5600 IU, tablets from Sandoz B.V.

The product is indicated for the treatment of postmenopausal osteoporosis in women who are not receiving vitamin D supplementation and are at risk of vitamin D insufficiency. The product 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 Fosavance 70 mg/ 5600 IU tablets. which has been centrally registered (EU/1/05/310/006-008) in the EEA by Merck Sharp & Dohme Ltd. Since 17 October 2007.

The concerned member states (CMS) involved in this procedure were Belgium, Bulgaria, Czech Republic, Germany, Estonia, Greece, Spain, France, Ireland, Italy, Latvia, Poland, Portugal, Romania and Slovenia.

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

II. QUALITY ASPECTS

II.1 Introduction

Alendroninezuur/Cholecalciferol Sandoz is a white to almost white, oval tablet debossed with 714 on one side. The tablet contains 70 mg of alendronic acid (as 91.350 mg sodium alendronate trihydrate) and 140 µg cholecalciferol (equivalent to 5600 IU vitamin D_3).

The tablets are packed in Alu/Alu blisters.

The excipients are: microcrystalline cellulose (E 460), crospovidone Type A (E 1202), magnesium stearate (E 470b), medium-chain triglycerides, modified starch (E 1450), sucrose, all Rac-α-tocopherol (E 307), sodium ascorbate and colloidal anhydrous silica (E 551).

II.2 Drug Substances

Sodium alendronate trihydrate
The active substance is sodium alendronate trihydrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white or almost white, crystalline powder which is sparingly soluble in water, practically insoluble in methanol and methylene chloride. Alendronate has five ionisable functional groups with pKa values across the whole pH range. In solution alendronate is present in the form of a zwitterion and is at intestinal physiological pH (pH 6–8) completely ionised. Only one crystalline form of alendronate sodium trihydrate is known.

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. An additional specification is applied for particle size distribution, which is tested with an in-house method. Batch analytical data demonstrating compliance with this specification have been provided for 3 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.

Cholecalciferol
The active substance is cholecalciferol concentrate (powder form), an established active substance described in the Ph.Eur. It is a white to yellowish powder. Cholecalciferol is practically insoluble in water. The lowest literature value is 7.7 µg/ml, which is sufficient for dissolution of 140 µg of cholecalciferol in 250 ml of water. Cholecalciferol has no ionisable functional groups between pH 1 to 14. For pure cholecalciferol no data are known about different polymorphic forms.

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 manufacturing process is adequately described. A flow chart was provided consisting of six steps. The starting material is acceptable as two CEPs have been granted for both sources of the starting material.

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 with additional tests for related substances, control of antioxidants and control of the particle size distribution. 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 by the ASMF holder for 14 batches of the active substance stored at 15°C (24 months), 25°C/60% RH (12 months) and 40°C/75% RH (6 months). The storage conditions 25°C/60% RH and 40°C/75% RH are in accordance with ICH conditions. Based on the data submitted, a retest period could be granted of 24 months with the storage condition: "Store below 15°C. Keep container tightly closed. Once opened, use contents quickly".
The MAH applied for a shelf-life of 24 months and a retest period of 3 months. Therefore, stability data have been provided by the ASMF holder for 2 batches stored at refrigerator temperature 2-8°C (9 months), 25°C/60% RH (6 months) and 40°C/75% RH (1 month). The tested parameters are sufficiently indicating stability. In view of the results, the retest period of 3 months with the storage condition: "Store below 15°C. Keep container tightly closed. Once opened, use contents quickly".

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 formulation development is based on comparison with the reference product Fosavance. A fixed composition and manufacturing process is applied. No design space has been claimed.
For each active substance a specific dissolution test is developed. The dissolution methods and specifications are acceptable also in view of the results of the batches used in the bioequivalence studies.

Dissolution data in aqueous media (pH 1.2, 4.5 and 6.8) have been provided. The dissolution of alendronate and cholecalciferol is faster for the test product Alendroninezuur/Cholecalciferol Sandoz than the reference product. As this situation was adequately explained and in view of the results of the bio-equivalence study, the difference in dissolution can be accepted.

Manufacturing process
The manufacturing process has been validated according to relevant European guidelines. The drug product is prepared by conventional dry granulation process with roller compaction. The process consists of blend preparation, dry granulation, blending and lubricating, and compressing. Suitable in-process controls are applied, where applicable, in line with the drug product specifications. Process validation data on the product have been presented for 4 full scale batches in accordance with the relevant European guidelines.

Control of excipients
Excipients microcrystalline cellulose (PH 112), crospovidone Type A and magnesium stearate comply with the current version of the monograph in Ph.Eur. 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 description, loss on drying, identity, assay, dissolution, related substances, assay and control of microbial quality. Documentation on the justification of the proposed limits for impurities of cholecalciferol has been provided. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from 5 production batches, including two bio batches, 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 for three production batches stored at 25°C/60% RH (24 months), 30°C/75% RH (12 months) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. The photostability studies according ICH conditions show that the product is sensitive to light. On basis of the data submitted, a shelf life was granted for 18 months with the storage condition: “Store below 25°C. Store in the original package in order to protect from light and moisture”.

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/Cholecalciferol Sandoz 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 Sandoz 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 Fosavance 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

Sodium alendronate trihydrate and cholecalciferol 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 member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted three bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted three bioequivalence studies in which the pharmacokinetic profile of the test product Alendroninezuur/Cholecalciferol Sandoz 70 mg/5600 IU, tablets (Sandoz B.V., NL) is compared with the pharmacokinetic profile of the reference product Fosavance (Merck Sharp & Dohme Ltd., UK):

- Study I - A bioequivalence study to evaluate alendronic acid under fasting conditions
- Study II - A bioequivalence study to evaluate cholecalciferol under fasting conditions
- Study III – An additional bioequivalence study to evaluate alendronic acid under fasting conditions

The choice of the reference product in the bioequivalence studies is accepted, as Fosavance has been registered through a centralised procedure. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Alendroninezuur/Cholecalciferol Sandoz may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of alendronic acid or cholecalciferol. 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 designs of the three studies are acceptable. The replicate study designs for study I and III are appropriate due to the high variability of alendronate in previous bioequivalence studies. The intra-subject variability was high (>30%) for the reference product. Therefore, as predefined in the protocol, the full replicate design allows the bioequivalence acceptance interval for C_{max}, to be widened to 69.84% - 143.19%.

Analytical/statistical methods
The analytical methods have been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in the three studies for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Bioequivalence studies

Bioequivalence study I: to evaluate alendronic acid under fasting conditions

Design

A single-dose, open-label, randomised, four-period, two-treatment, two-sequence, crossover, replicate bioequivalence study was carried out under fasted conditions in 60 healthy male (n=29) and female (n=31) subjects, aged 18-55 years. Each subject received a single dose (70 mg alendronic acid, 5600 IU cholecalciferol) of one of the 2 active substances formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were 4 dosing periods, separated by a washout period of 7 days. Subjects were randomly assigned to one of the two dosing sequences ABAB or BABA.

Blood samples were collected pre-dose and at 0.167, 0.33, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.33, 2.67, 3, 4, 5, 6 and 8 hours after administration of the products.

Results

Three subjects completed at least two periods of the study resulting in administration of the reference product and one test product. In accordance with the protocol, all three subjects were included in the pharmacokinetic and statistical analyses. Overall, 60 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=118	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	59.1 ± 57.5**	62.3 ± 61.6***	21.1 ± 20.0**	1.0 (0.33 – 3.0)**	1.7 ± 0.2**
Reference	45.3 ± 38.1	47.6 ± 40.2	16.4 ± 12.6	1.0 (0.33 – 3.0)	1.7 ± 0.2
***Ratio (90% CI)**	1.20 (1.08 – 1.35)	--	1.18 (1.06 – 1.31)	--	--
CV (%)	55	--	54	--	--

$AUC_{0-\infty}$ 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*
** *N=117*
*** *N=116*

Bioequivalence study II: to evaluate cholecalciferol under fasting conditions

Design

A single-dose, open-label, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 28 healthy male (n=16) and female (n=12) subjects, aged 18-55 years. Each subject received a single dose (70 mg alendronic acid, 5600 IU cholecalciferol) of one of the 2 active substances formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were 2 dosing periods, separated by a washout period of 14 days. Consumption of foods and drinks high in vitamin D (fish, eggs, milk (including goat's milk), cheese, yogurt, margarine, fortified orange juice, and soy and rice beverages) was restricted from 10 days prior to drug administration in period 1 until the last sample of the study was collected. Subjects were instructed to avoid prolonged exposure to direct sunlight from 10 days prior to drug administration in period 1 until after the last blood sample of the study was collected. Subjects were advised to wear clothing to cover their neck, torso, arms, and legs during this time.

Blood samples were collected at pre-dose and at 3, 5, 7, 9, 11, 12, 13, 14, 15, 16, 18, 20, 22, 24, 30, 36, 48 and 72 hours after administration of the products.

Results
Two subjects withdrew from the study due to an adverse event (vomiting) and diarrhoea. In total, 26 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=26	**AUC_{0-h}** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	303 ± 71	8.5 ± 1.8	14.0 (11.17 - 20.0)
Reference	295 ± 58	8.2 ± 1.6	14.0 (11.0 – 18.0)
***Ratio (90% CI)**	1.02 (0.96 – 1.08)	1.03 (0.96 – 1.10)	--
CV (%)	12	14	--
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 **CV** coefficient of variation			

**ln-transformed values*

Bioequivalence study III: to evaluate alendronic acid under fasting conditions
Design
A single-dose, open-label, randomised, four-period, two-treatment, two-sequence, crossover, replicate bioequivalence study was carried out under fasted conditions in 100 healthy male (n=44) and female (n=56) subjects, aged 20-55 years. Each subject received a single dose (70 mg alendronic acid, 5600 IU cholecalciferol) of one of the 2 active substances formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were 4 dosing periods, separated by a washout period of 7 days. Subjects were randomly assigned to one of the two dosing sequences ABAB or BABA.

Blood samples were collected pre-dose and at 0.167, 0.33, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.33, 2.67, 3, 4, 5, 6 and 8 hours after administration of the products.

Results
One subject was withdrawn from the study due to emesis prior to period 2.One subject was withdrawn prior to period 3 due to non-compliance (positive urine benzodiazepines). In addition, three subjects were withdrawn prior to period 4 due to non-compliance (positive urine cannabis and cotinine), personal reasons and adverse events. Subjects who completed two or more periods, were included in the pharmacokinetic analysis. Therefore, 99 subjects were included.

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

Treatment N=196 (test) =194 (ref.)	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	48.9 ± 41.9	49.1 ± 44.3	17.0 ± 15.0	1.0 (0.33 – 2.0)	1.6 ± 0.2
Reference	45.3 ± 40.9	47.5 ± 43.9	16.4 ± 13.8	1.0 (0.33 – 2.33)	1.6 ± 0.3
***Ratio (90% CI)**	1.01 (0.94 – 1.0)	--	1.00 (0.93 – 1.07)	--	--
CV (%)	47	--	43	--	--

$AUC_{0-\infty}$	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 studies:
In study I, alendronate was found to be highly variable for AUC_{0-t} and C_{max} with an intra-subject variability of 55% and 54%. Widening of the acceptance intervals was allowed for C_{max}. The 90% confidence interval calculated for C_{max} is within the bioequivalence acceptance range of 69.84% - 143.19%. With regard to the extent of absorption, the Reference and Test product were considered not bioequivalent. The 90% confidence interval calculated for $AUC_{(0-t)}$, (1.08 – 1.35) was outside the normal range of acceptability (0.80 – 1.25).

In study II and III, the 90% confidence intervals calculated for AUC_{0-t} and C_{max} were inside the normal range of acceptability (0.80 – 1.25).

Based on the study results of the submitted bioequivalence studies Alendroninezuur/Cholecalciferol Sandoz 70 mg/5600 IU, tablets is considered bioequivalent with Fosavance 70 mg/ 5600 IU tablets.

The MEB has been assured that the bioequivalence studies have 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 Sandoz.

- Summary table of safety concerns as approved in RMP

Important identified risks	- Oesophageal adverse experience - Osteonecrosis of the jaw
Important potential risks	- Atypical femoral fractures
Missing information	- Use during pregnancy and lactation - 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 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. The test consisted of: two rounds with 12 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.

The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Alendroninezuur/Cholecalciferol Sandoz 70 mg/5600 IU, tablets has a proven chemical-pharmaceutical quality and is a generic form of Fosavance 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 Sandoz with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 22 June 2016.

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
NL/H/3578/1/IB/001	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product; Implementation of change(s) for which no new additional data is required to be submitted by the MAH	SmPC PL	12-01-2017	Approved	-