LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Actibon
(cholecalciferol, sodium alendronate trihydrate, alendronic acid)

SE/H/2353/01-02/DC

This module reflects the scientific discussion for the approval of Actibon. The procedure was finalised on 2024-02-28. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Actibon, 70 mg/2800 IE, 70 mg/5600 IE, Tablet.

The active substance is cholecalciferol, sodium alendronate trihydrate, alendronic acid. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Actibon, 70 mg/2800 IE, 70 mg/5600 IE, Tablet, is a generic application submitted according to Article 10(1) of Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and CY, EL as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is FOSAVANCE 70 mg/2,800 IU tablets authorised in Union since 2005, with N.V. Organon as marketing authorisation holder.

The reference product used in the bioequivalence study is FOSAVANCE 70 mg/5,600 IU tablets from Germany with N.V. Organon as marketing authorisation holder.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of alendronic acid/cholecalciferol are well known. As alendronic acid/cholecalciferol is widely used, well-known active substances, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Actibon is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Actibon from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted one bioequivalence study comparing Actibon (Alendronic acid/Cholecalciferol) with the reference product Fosavance.

Pharmacokinetic properties of the active substances

Alendronate
Absorption:
Relative to an intravenous reference dose, the oral mean bioavailability of alendronate in women was 0.64% for doses ranging from 5 to 70 mg when administered after an overnight fast and two hours before a standardised breakfast. Bioavailability was decreased similarly to an estimated 0.46% and 0.39% when alendronate was administered one hour or half an hour before a standardised breakfast. In osteoporosis studies, alendronate was effective when administered at least 30 minutes before the first food or beverage of the day.

Bioavailability was negligible whether alendronate was administered with, or up to two hours after, a standardised breakfast. Concomitant administration of alendronate with coffee or orange juice reduced bioavailability by approximately 60%.

In healthy subjects, oral prednisone (20 mg three times daily for five days) did not produce a clinically meaningful change in oral bioavailability of alendronate (a mean increase ranging from 20% to 44%).

Elimination
The terminal half-life in humans is estimated to exceed ten years, reflecting release of alendronate from the skeleton.

Cholecalciferol
Absorption:
In healthy adult subjects (males and females), following administration of alendronic acid and cholecalciferol combination 70 mg/2800 IU tablets after an overnight fast and two hours before a meal, the mean area under the serum-concentration-time curve ($AUC_{0\text{-}120\ hrs}$) for vitamin D_3

(unadjusted for endogenous vitamin D_3 levels) was 296.4 ng•hr/ml. The mean maximal serum concentration (C_{max}) of vitamin D_3 was 5.9 ng/ml, and the median time to maximal serum concentration (t_{max}) was 12 hours.

In healthy adult subjects (males and females), following administration of alendronic acid and cholecalciferol combination 70 mg/5,600 IU after an overnight fast and two hours before a meal, the mean area under the serum-concentration-time curve ($AUC_{0\text{-}80\ hrs}$) for vitamin D_3 (unadjusted for endogenous vitamin D_3 levels) was 490.2 ng•hr/ml. The mean maximal serum concentration (C_{max}) of vitamin D_3 was 12.2 ng/ml and the median time to maximal serum concentration (t_{max}) was 10.6 hours.

Elimination:
The mean half-life of vitamin D_3 in the serum following an oral dose of alendronic acid and cholecalciferol combination (70 mg/2800 IU) is approximately 24 hours.

Study 825-13
Methods
This was a single-dose, two-way crossover study conducted in 126 healthy volunteers (110 subjects completed), comparing Alendronic acid/Cholecalciferol, 70 mg/5600 IU, tablet with Fosavance, 70 mg/5600 IU, tablet under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 24 hours (alendronate) and 96 hours (cholecalciferol) post-dose. Plasma concentrations of alendronate and cholecalciferol were determined with LC-MS/MS methods. Analysis of variance (ANOVA) was performed on the log-transformed data for $AUC_{0\text{-}t}$ and C_{max}. The study was conducted between 22 August 2014 and 15 September 2014.

Results
The results from the pharmacokinetic and statistical analysis are presented below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for alendronate, n=110.

Treatment	$AUC_{0\text{-}t}$ ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**173.3 ± 95.0**	**61.4 ± 37.0**	**1.0 (0.5 - 2.5)**
Reference	**175.7 ± 99.3**	**60.8 ± 36.8**	**1.0 (0.5 - 2.0)**
***Ratio (90% CI)**	**101.8 (94.07-110.16)**	**103.8 (95.23-113.14)**	**-**

$AUC_{0\text{-}t}$ area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for cholecalciferol (baseline corrected data), n=110.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**375.7 ± 133.6**	**10.5 ± 3.4**	**11.0 (8.0 - 18.0) n=109**
Reference	**392.3 ± 133.8**	**11.1 ± 3.3**	**10.0 (7.0 - 18.0)**
***Ratio (90% CI)**	**97.2 (91.00-103.87)**	**95.1 (90.30-100.11)**	**-**

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 plasma concentration

**calculated based on ln-transformed data*

For both alendronate and baseline corrected cholecalciferol AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

The data of baseline uncorrected cholecalciferol was provided for supportive information only.

A biowaiver was sought for the additional strength of 70 mg/2800 IU.

Discussion and overall conclusion
The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr). The bioanalytical methods were adequately validated.

Based on the submitted bioequivalence study, Actibon is considered bioequivalent with Fosavance.

Based on submitted PK data, there is no indication of non-linear pharmacokinetics (less than proportional increase in AUC with increasing dose) over the dose interval 2800-5600 IU that would require an additional study of the lower strength. Thus, absence of study with the lowest tablet strength 70 mg/2800 IU can be accepted from a pharmacokinetic perspective.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

Pharmacovigilance system
The Applicant has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable

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 Actibon.

Part II Safety specification
The MAH has submitted the version 1.0 RMP dated 2023-06-12 and proposed the following summary safety concerns:

Important Identified Risks	• Osteonecrosis of the jaw • Oesophageal adverse experiences
Identified potential risks	• Atypical femur fracture
Missing information	• Use in children and adolescents • Use in patients with severe renal impairment • Use in pregnancy and lactation

Assessor's comment: Having considered the data in the safety specification and that it is in line with other approved alendronic acid/cholecalciferol products including a product on the list of safety concerns published on the CMDh website, the assessor agrees that the safety concerns listed by the MAH are appropriate.

Part III Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Part V Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Part VI Summary of the RMP
The Summary of the RMP is endorsed.

Conclusion of RMP assessment
The submitted Risk Management Plan, version 1.0 signed 2023-06-12 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

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 language used for the purpose of user testing the PL was English.

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

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Actibon, is found adequate. There are no objections to approval of Actibon, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Actibon, 70 mg/2800 IE, 70 mg/5600 IE, Tablet was positively finalised on 2024-02-28.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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