LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Alendronat Sandoz

(Sodium alendronate)

SE/H/704/01/DC

This module reflects the scientific discussion for the approval of Alendronat Sandoz. The procedure was finalised at 2008-02-25. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Sandoz A/S has applied for a marketing authorisation for Alendronat Sandoz Veckotablett film-coated tablets 70 mg claiming essential similarity to Fosamax tablets 70 mg marketed the EU by Merck Sharp & Dohme. The product contains sodium alendronate as active substance. For approved indications see the Summary of Product Characteristics. The reference product used in the bio-equivalence study is Fosamax tablets marketed by Merck Sharp & Dohme in Germany.

II. QUALITY ASPECTS

II.1 Introduction

Alendronat Sandoz Veckotablett is presented in the form of film-coated tablets containing 91.36 mg spdoium alendronate which corresponds to 70 mg of the alendronic acid. The excipients are microcrystalline cellulose, croscarmellose sodium, sodium lactate and magnesium stearate. The tablets are packed in blister.

II.2 Drug Substance

Sodium alendronate has a monograph in the Ph Eur.

Sodium alendronate is a white or almost white, crystalline powder which is soluble in water, very slightly soluble in methanol and practically insoluble in methylene chloride. The structure of sodium alendronate has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on polymorphism and chirality is presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

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

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Alendronat Sandoz Veckotablett tablets are formulated using excipients described in the current Ph Eur. All raw materials used in the product of animal origin has demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01).

The product development has taken into consideration the physico-chemical characteristics of the active substance, such as local irritation in the oesophagus.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

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 under ICH conditions have been performed and data presented support the shelf life claimed in the SPC. This medicinal product does not require any special storage conditions.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approval based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

To support the application, the applicant has submitted one randomised 2-period, 2-treatment, single-dose, cross-over bioequivalence study under fasting conditions. In each period a single dose of 70 mg alendronate was administered, either as the generic test product or as the reference product (Fosamax 70 mg film-coated tablet, MSD, Germany). Subjects were fasted for 4 hours postdose. Urine was collected during 14 time intervals up to 72 hours postdose. Urine samples were stored at -20ºC until analysis. There was a 21-day washout between treatment periods.

Due to the low bioavailability of alendronate, plasma concentrations may often be below limit of detection after a normal oral dose. Pharmacokinetic assessments were therefore based on urinary excretion of alendronate. This is acceptable, since there is no biotransformation of alendronate and urinary excretion is the predominant route of elimination. The primary variables for assessment of bioavailability were therefore cumulative urinary excretion (Ae_{0-72}), as a measure of plasma AUC, and maximum rate of urinary excretion (R_{max}) as a measure of plasma C_{max}. Pre-specified criteria for concluding bioequivalence were 90% confidence intervals within 80%-125% for Ae_{0-72} and within 70%-143% for R_{max}.

The analysis method for detection of alendronate in urine was adequately validated. Satisfactory method performance during study sample analysis was demonstrated.

The pharmacokinetic and statistical results are shown in Table 1. Bioequivalence was demonstrated between the test and reference products with 90% CI for the test/reference ratio within 80%-125% for both Ae_{0-72hr} and R_{max}.

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

Treatment	AUC_{0-72} (µg)	R_{max} (µg/hr)	t_{max} (hr)
Test	325.55 ± 285.12	97.74 ± 71.40	1.10 (0.58 - 4.95)
Reference	310.12 ± 257.98	94.68 ± 72.56	1.43 (0.58 - 3.45)
Ratio (90% CI)[1]	101.1%	102.12%	ns[2]
CV (%)	89.9% - 113.7%	91.8% - 113.6%	

[1] ln-transformed values
[2] No significant difference in T_{max} according to Wilcoxon's test

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User testing of the package leaflet has been performed.

The SPC, package leaflet and labelling are acceptable.

The risk/benefit ratio is considered positive and Alendronat Sandoz Veckotablett 70 mg film-coated tablets is recommended for approval.

Specific obligations, follow-up measures, (if applicable)

VI.
VII. APPROVAL

The Decentralised procedure for Alendronat Sandoz Veckotablett 70 mg film-coated tablets was successfully finalised on 2008-02-25.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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