LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Alenpol Veckotablett
(sodium alendronate)

SE/H/1223/01/MR

This module reflects the scientific discussion for the approval of Alenpol Veckotablett. The procedure was finalised at 2012-05-23. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Pharmaceutical Works Polpharma S.A has applied for a marketing authorisation for Alenpol Veckotablett 70 mg tablet claiming essential similarity to Fosamax, 70 mg, tablets marketed in Sweden by Merck Sharp & Dohme B.V. The product contains alendronate as active substance. For approved indications see the Summary of Product Characteristics. The reference product used in the bio-equivalence study is Fosamax, 70 mg, tablets marketed by Merck Sharp & Dohme in UK.

II. QUALITY ASPECTS

II.1 Introduction

Alenpol Veckotablett, 70 mg, tablets is presented in the form of tablets containing 91.36 mg of sodium alendronate (trihydrate) which corresponds to 76.16 mg sodium alendronate and 70 mg of alendronic acid, respectively. The excipients are lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, silica colloidal anhydrous and magnesium stearate.
The tablets are packed in aluminium/PVC blister packs.

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 freely soluble in water, very slightly soluble in methanol, practically insoluble in methylene chloride. The structure of sodium alendronate has been adequately proven and its physico-chemical properties sufficiently described. 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

Alenpol Veckotablett, 70 mg, tablets is formulated using excipients described in the current Ph Eur. All raw materials used in the product are of vegetable origin or in the case of lactose 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.

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, with no special storage precautions.

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 approved 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

The application is supported by an appropriately designed bioequivalence study (study code 30263). It was a two-way, cross-over single dose study in fasting healthy voluteers, men and postmenopausal or surgically sterilised women. Seventy-six subjects completed the study and were included in the data set for statistical analysis.

The clinical part of the study was performed at Anapharm Inc, Montreal, Canada between Oct 6 and Oct 31 2003. The analytical and statistical part was performed at Anapharm Inc, Sante-Foy, Canada. Urine samples were analysed between Nov 19 and Dec 17, 2003. The analysis method was adequately validated.

Pharmacokinetic assessments were based on urinary excretion of alendronate. Since there is no biotransformation of alendronate and since urinary excretion is the predominant route of elimination, it is scientifically adequate to use urinary excretion data instead of plasma concentration data. It is also considered established that C_{max} is not important for either efficacy or safety of bisphosphonates, based on e.g. the possibility to dose them once weekly or once daily. In addition, the urinary sampling in the initial post-dose period of the performed study is frequent, thus making R_{max} a reliable measure of C_{max}. Although measurement of plasma data would have been preferred, it is not considered justified to request an additional study with plasma samples for this product. Thus, the use of urinary data is considered acceptable in this case.

The primary variables for assessment of bioavailability were specified in the protocol as cumulative urinary excretion (Ae_{0-36}) and maximum rate of urinary excretion (R_{max}). Secondary parameter was time of maximal urinary excretion rate (T_{max}).

Test formulation was Alendronate 70 mg film-coated tablet, Pharmaceutical Works Polpharma, PL, Batch no. 10703, expiry date July 2005.
Reference formulation was Fosamax 70 mg film-coated tablet from Merck, Sharp & Dohme, UK, Batch no. E3010A, expiry date Sept 2009.

The pharmacokinetic and statistical results for urinary excretion of alendronate are shown in Table 1.

Table 1. Mean (SD) urinary pharmacokinetic parameters for alendronate (n=76) and statistical analysis for bioequivalence

Preparation	R_{max} (µg/h)	T_{max}* (h)	Ae_{0-36} (µg)
Test	65.28 ± 46.05	0.60 (0.11 - 2.48)	202.24 ± 140.01
Reference	69.11 ± 57.60	0.85 (0.57 - 3.45)	219.12 ± 238.87
Ratio test/ref	94.08%	na	97.57%
90% CI	83.71% - 105.74%	na	86.73% - 109.77%

* T_{max} is given as median (range)

Based on the results, the test and reference formulations can be concluded to be bioequivalent in terms of systemic exposure (determined as Ae_{0-36}) and rate of absorption (determined as R_{max}).

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 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 PIL 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.

The risk/benefit ratio is considered positive and Alenpol Veckotablett 70 mg tablet is recommended for approval.

VI. APPROVAL

The Mutual recognition procedure for Alenpol Veckotablett 70 mg tablet was successfully finalised on 2012-05-23.

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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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