LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Alendronat Hexal
(Sodium alendronate trihydrate)

SE/H/517/01-02

This module reflects the scientific discussion for the approval of Alendronat Hexal. The procedure was finalised at 2006-05-09 (70 mg) and 2007-01-22 (10 mg tablet). For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

HEXAL A/S has applied for a marketing authorisation for Alendronat HEXAL, tablets, 10 mg and 70 mg claiming essential similarity to Fosamax, tablets, 10 mg and 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 10 mg and 70 mg marketed by Merck Sharp & Dohme, UK.

The procedure concerning the 10 mg tablet was referred to CMD as one MS could not accept the indication “Treatment of osteoporosis in men” and another MS had Major Objections on the same indication plus also on the proposed indication “Prophylaxis of corticosteroid-induced osteoporosis”. After discussion at the CMD meeting, the indication “Prophylaxis of corticosteroid-induced osteoporosis” was accepted by all MS while the disagreement concerning the indication “Treatment of osteoporosis in men” persisted. The RMS suggested the indication “Treatment of osteoporosis in men at high risk of fractures” that could be accepted by all MS but as the MAH was not prepared to accept this narrowing of the indication in male osteoporosis, no consensus could be reached concerning the indication in men during the procedure and the 10 mg tablet was referred to CHMP.

Following CHMP referral, unity was reached on the following indication for male osteoporosis:
“Treatment of osteoporosis in men at increased risk of fracture. A reduction in the incidence of vertebral, but not of non-vertebral fractures has been demonstrated.”

II. QUALITY ASPECTS

II.1 Introduction

Alendronat HEXAL is presented in the form of tablets containing 13.05 or 91.36 mg of sodium alendronate (trihydrate) which corresponds to 10 or 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 HEXAL 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, when stored below 25°C in the original package.

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

The ratio between amounts of active substance and excipients is not the same between the 10 and 70 mg tablet in the test product. Therefore, the Applicant performed two bioequivalence studies comparing the 10 and 70 mg tablets of the test product, respectively, with the originator Fosamax 10 and 70 mg tablets, and one study evaluating bioequivalence between the two tablet strengths.

Due to the low and variable bioavailability and the rapid clearance from plasma of alendronate, which results in undetectable plasma concentrations, the Applicant chose to compare release properties of the generic tablet and the originator based on measurement of unchanged drug excreted in urine.

The pharmacokinetic and statistical results of the comparison between the Alendronat Arrow 70 mg tablet and the Fosamax 70 mg tablet are shown in tables 1 and 2, respectively.

Table 1. Urinary excretion pharmacokinetics of alendronate after administration of one 70 mg test tablet or one 70 mg Fosamax tablet.

	Test product 70 mg (test)			**Fosamax 70 mg (reference)**		
	mean	*SD*	*CV (%)*	*mean*	*SD*	*CV (%)*
Ae_{0-36} (µg)	377.95	239.40	63.34	412.98	353.75	85.66
R_{max} (µg/hr)	113.35	70.45	62.15	125.44	94.05	74.97
	median	*IQR*		*median*	*IQR*	
T_{max} (hr)	1.43	0.36		1.43	0.85	

SD, standard deviation; CV, coefficient of variation; IQR, interquartile range

Table 2. Bioequivalence results for test tablet 70 mg vs. Fosamax 70 mg tablets

Test vs. Reference	**Ae_{0-36}**	**R_{max}**
Ratio of least-square means	94.09 %	92.14 %
90% geometric CI	85.55% - 103.48%	83.80% to 101.30%

The pharmacokinetic and statistical results of the comparison between the test 10 mg tablet and the Fosamax 10 mg tablet are shown in tables 3 and 4, respectively.

Table 3. Urinary excretion pharmacokinetics of alendronate after administration of 40 mg alendronate as test tablets 4x10 mg or Fosamax 4x10 mg.

	Test product 4x10 mg (test)			**Fosamax 4x10 mg (reference)**		
	mean	*SD*	*CV (%)*	*mean*	*SD*	*CV (%)*
Ae_{0-36} (µg)	105.0	98.0	93.3	101.4	72.8	71.8
R_{max} (µg/hr)	35.9	33.8	94.1	36.4	28.0	76.7
	median	*IQR*		*median*	*IQR*	
T_{max} (hr)	1.43	0.86		0.61	0.86	

SD, standard deviation; CV, coefficient of variation; IQR, interquartile range

Table 4. Bioequivalence results for test tablet 10 mg vs. Fosamax 10 mg tablets

Test vs. Reference	**Ae_{0-36}**	**R_{max}**
Ratio of least-square means	99.5%	95.7%
90% geometric CI	91.1 - 108.8%	87.7 - 104.6%

The pharmacokinetic and statistical results of the comparison between test 10 mg and 70 mg tablets are shown in tables 5 and 6, respectively.

Table 5. Urinary excretion pharmacokinetics of alendronate after administration of test product as 1x70 mg or as 7x10 mg

	Test product 1x70 mg			**Test product 7x10 mg**		
	mean	*SD*	*CV (%)*	*mean*	*SD*	*CV (%)*
Ae_{0-36} (µg)	336.3	220.9	65.7	292.4	161.7	55.3
R_{max} (µg/hr)	102.1	64.5	63.2	90.2	51.9	57.5
	median	*IQR*		*median*	*IQR*	
T_{max} (hr)	1.43	0.86		1.43	0.85	

SD, standard deviation; CV, coefficient of variation; IQR, interquartile range

Table 6. Bioequivalence results for test 1x70 mg vs. 7x10 mg

70 mg tablet vs. 10 mg tablet	**Ae_{0-36}**	**R_{max}**
Ratio of least-square means	110.5 %	109.0 %
90% geometric CI	102.0 - 119.8 %	100.0 - 118.9 %

Bioequivalence in terms of systemic exposure (determined as Ae_{0-36}) and rate of absorption (determined as R_{max}) was demonstrated in all studies since the 90% confidence intervals for the test/reference ratio fell within 80-125%.

IV.2 Discussion on the clinical aspects

This product has been shown to be essentially similar and refers to a product approved based on a full application with regard to clinical efficacy/safety data. For the CMD and CHMP referral procedures on the 10 mg tablet, literature data were submitted and assessed.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User testing of the package leaflet for Alendronat Hexal Veckotablett 70 mg has been performed and the results showed that the package leaflet is well written and understandable for the patients. The package leaflet for Alendronat Hexal 10 mg is structured in the same way as the leaflet for 70 mg and a separate testing of that leaflet is therefore not considered necessary.

The SPC, package leaflet and labelling are acceptable.

The risk/benefit ratio is considered positive and Alendronat Hexal, 10 mg and 70 mg (Veckotablett) tablets is recommended for approval.

VI. APPROVAL

The Mutual recognition/Decentralised procedure for Alendronat Hexal 10 mg and 70 mg tablets was successfully finalised on 2006-05-09 (70 mg tablet) and 2007-01-22 (10 mg tablet).

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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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