

IPAR



**PUBLIC ASSESSMENT REPORT FOR A
MEDICINAL PRODUCT FOR HUMAN USE**

Scientific discussion

Romax Once Weekly 70mg Tablets

Sodium Alendronate

PA1445/017/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority, (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Alendronic Acid Ceft 10mg Tablets and Alendronic Acid Ceft Once Weekly 70mg Tablets from Ceft Limited on 7th October 2011 for the following indications:

A transfer application was submitted approved in July 2012, this involved a change in the marketing authorisation holder, marketing authorisation number and name of the product.

Alendronic Acid Aurobindo 10mg Tablets

- In post-menopausal women with osteoporosis, Alendronic acid Ceft is indicated for the treatment of osteoporosis to prevent fractures, including those of the hip and spine (vertebral compression fractures).
- Alendronic acid Ceft is indicated for the treatment of osteoporosis in men to prevent fractures.
- Alendronic acid Ceft is indicated for the treatment and prevention of glucocorticoid-induced osteoporosis in men and women.
- In post-menopausal women who are at risk of developing osteoporosis Alendronic acid Ceft is indicated for the prevention of osteoporosis to reduce the risk of future fracture.

Romax Once Weekly 70mg Tablets

- Treatment of postmenopausal osteoporosis. Alendronic acid reduces the risk of vertebral and hip fractures.

This application for a marketing authorisation was submitted in accordance with Article 10.1 Generic Application. The reference medicinal products are Fosamax 10mg Tablet PA 35/83/1 and Fosamax Once Weekly 70mg Tablet PA 35/80/3, both marketed by Merck Sharpe & Dohme Limited.

The Summary of Product Characteristics for (SPC) for this medicinal product is available on the HPRA's website at www.hpra.ie

Name of the product	Alendronic Acid Aurobindo 10mg Tablets Romax Once Weekly 70mg Tablets
Name of the active substance (INN)	Sodium Alendronate
Pharmacotherapeutic classification (ATC code)	M05BA04
Pharmaceutical form and strengths	10mg & 70mg Tablets
Marketing Authorisation Number(s) in Ireland (PA)	PA1445/017/001
Marketing Authorisation Holder	Aurobindo Pharma (Malta) Limited

The method of sale and Supply for these medicinal products will be prescription only medicines (Category B – Medicinal products which may be renewed) with supply through pharmacies only and promotion to healthcare professionals only.

The Summary of Product Characteristics for (SPC) for this medicinal product is available on the HPRA's website at <http://www.hpra.ie/>

II QUALITY ASPECTS

II.1. Introduction

This application is for Alendronic Acid Aurobindo 10mg Tablets and Romax Once Weekly 70mg Tablets.

II.2 Drug substance

The active substance is sodium alendronate, an established active substance described in the European Pharmacopoeia, and is

manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

Alendronic Acid Aurobindo 10mg Tablets and Romax Once Weekly 70mg Tablets are uncoated tablets. Each tablet is a white to off-white, round(10 mg), oval (for 70 mg), biconvex uncoated tablet debossed with 'F' on one side and either '18' or '21' on the other side, depending on the strength. The tablets contain sodium alendronate equivalent to either 10mg or 70mg of alendronic acid. The other excipients in the tablets are microcrystalline cellulose, maize starch, sodium starch glycolate, povidone and magnesium stearate.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European and ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for Tablets, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

Alendronic Acid Aurobindo 10mg Tablets are presented in blister strips of PVC/Aclar/Aluminium in pack sizes of 10, 14, 20, 28, 30, 50, 56, 60, 84, 90, 98, 100, 112, 140 and 250 tablets. Alendronic Acid Ceft 10mg Tablets are also marketed in HDPE containers with polypropylene lids, in pack sizes of 30, 50, 100, 250 and 1000 tablets.

Romax Once Weekly 70mg Tablets are presented in blister strips of PVC/PE/PVdC - Aluminium in pack sizes of 2, 4, 8, 12, 20, 30, 40, 50 or 60 tablets.

Evidence has been provided that the blister strips and HDPE containers comply with Ph. Eur. requirements and EU legislation for use with foodstuffs.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines demonstrating the stability of the product for 3 years with no special storage conditions.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Alendronic Acid Aurobindo 10mg Tablets and Romax Once Weekly 70mg Tablets.

III NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Fosamax of Merck Sharp & Dohme on the European market. No new preclinical data have been submitted. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

III.2 Ecotoxicity/environmental risk assessment

Since alendronic acid 10 mg and 70 mg tablets are generic medicinal products, the possibility of the risks to the environment from the point of view of their use are expected to be the same as those of the originator product. An in-depth environmental risk assessment was not performed.

III.3 Discussion on the non-clinical aspects

No new preclinical data were submitted as this application was an abridged application, relying on preclinical data from the originator product. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

IV CLINICAL ASPECTS

IV.1 Introduction

Alendronic acid (as sodium alendronate) is a well known active substance with established efficacy and tolerability.

The content of the SPC approved during the national/ procedure is in accordance with that accepted for the reference product Fosamax marketed by Merck Sharp and Dohme Limited.

The Applicant conducted a fully GLP/GCP compliant open label, randomized, two treatment, two sequence, two period, cross-over, single-dose comparative oral bioavailability study of alendronic acid 70 mg tablets (Test) of Aurobindo Pharma Ltd., India and Fosamax® 70 mg tablets (Reference) of laboratories Merck Sharp & Dohme, France, in 150 healthy, adult, male and female human subjects under fasting conditions.

Based on the pharmacokinetic parameters of active substance the reference tablet Fosamax 70mgs marketed by Merck Sharp & Dohme and test tablet alendronic acid 70 mg tablets (Test) of Aurobindo Pharma Ltd are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The pharmacokinetics of the active substance are linear.

The Applicant has provided sufficient justification for a biowaiver for the lower 10mg strength as the conditions for a biowaiver set out in the guideline on bioequivalence were met.

Therefore the results of the bioequivalence study performed with the 70mg tablets apply to the 10mg tablet strength and a separate bioequivalence study examining the pharmacokinetics of the 10mg strength is not necessary.

The content of the SPC approved during the national/ procedure is in accordance with that accepted for the reference product Fosamax marketed by Merck Sharp & Dohme.

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

Absorption

Relative to an intravenous (IV) reference dose, the oral bioavailability of alendronate in women was 0.7% for doses ranging from 5 to 40 mg when administered after an overnight fast and two hours before a standardised breakfast. Oral bioavailability in men (0.6%) was similar to that in women. Bioavailability was decreased similarly (by approximately 40%) whether alendronate was administered one hour or half an hour before a standardised breakfast. In osteoporosis studies, alendronic acid 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 the oral bioavailability of alendronate (a mean increase ranging from 20 to 44%).

Distribution

Studies in rats show that alendronate transiently distributes to soft tissues following 1 mg/kg IV administration but is then rapidly redistributed to bone or excreted in the urine. The mean steady-state volume of distribution, exclusive of bone, is at least 28 litres in humans. Concentrations of drug in plasma following therapeutic oral doses are too low for analytical detection (<5 ng/ml). Protein binding in human plasma is approximately 78%.

Biotransformation

There is no evidence that alendronate is metabolised in animals or humans.

Elimination

Following a single IV dose of [¹⁴C] alendronate, approximately 50% of the radioactivity was excreted in the urine within 72 hours and little or no radioactivity was recovered in the faeces. Following a single 10 mg IV dose, the renal clearance of alendronate was 71 ml/min, and systemic clearance did not exceed 200 ml/min. Plasma concentrations fell by more than 95% within 6 hours following IV administration. The terminal half-life in humans is estimated to exceed ten years, reflecting release of alendronate from the skeleton. Alendronate is not excreted through the acidic or basic transport systems of the kidney in rats, and thus it is not anticipated to interfere with the excretion of other drugs by those systems in humans.

Characteristics in patients

Preclinical studies show that the drug that is not deposited in bone is rapidly excreted in the urine. No evidence of saturation of bone uptake was found after chronic dosing with cumulative IV doses up to 35 mg/kg in animals. Although no clinical information is available, it is likely that, as in animals, elimination of alendronate via the kidney will be reduced in patients with impaired renal function. Therefore, somewhat greater accumulation of alendronate in bone might be expected in patients with impaired renal function (see 4.2 'Posology and method of administration').

IV.3 Pharmacodynamics

Pharmacotherapeutic group: Drugs affecting bone structure and mineralisation, biphosphonate.

ATC Code: M05B A04

Alendronic acid is a bisphosphonate that inhibits osteoclastic bone resorption with no direct effect on bone formation. The bone formed during treatment with alendronic acid is of normal quality.

Treatment of post-menopausal osteoporosis

The effects of alendronic acid on bone mass and fracture incidence in post-menopausal women were examined in two initial efficacy studies of identical design (n=994) as well as in the Fracture Intervention Trial (FIT: n=6,459).

In the initial efficacy studies, the mean bone mineral density (BMD) increases with alendronic acid 10 mg/day relative to placebo at three years were 8.8%, 5.9% and 7.8% at the spine, femoral neck and trochanter, respectively. Total body BMD also increased significantly. There was a 48% reduction in the proportion of patients treated with alendronic acid experiencing one or more vertebral fractures relative to those treated with placebo. In the two-year extension of these studies BMD at the spine and trochanter continued to increase and BMD at the femoral neck and total body were maintained.

FIT consisted of two placebo-controlled studies: a three-year study of 2,027 patients who had at least one baseline vertebral (compression) fracture and a four-year study of 4,432 patients with low bone mass but without a baseline vertebral fracture, 37% of whom had osteoporosis as defined by a baseline femoral neck BMD at least 2.5 standard deviations below the mean for young,

adult women.

In all FIT patients with osteoporosis from both studies, alendronic acid reduced the incidence of: ≥ 1 vertebral fracture by 48%, multiple vertebral fractures by 87%, ≥ 1 painful vertebral fracture by 45%, any painful fracture by 31% and hip fracture by 54%.

Overall these results demonstrate the consistent effect of alendronic acid to reduce the incidence of fractures, including those of the spine and hip, which are the sites of osteoporotic fracture associated with the greatest morbidity.

Prevention of post-menopausal osteoporosis

The effects of alendronic acid to prevent bone loss were examined in two studies of post-menopausal women aged 60 years. In the larger study of 1,609 women (≥ 6 months post-menopausal) those receiving alendronic acid 5 mg daily for two years had BMD increases of 3.5%, 1.3%, 3.0% and 0.7% at the spine, femoral neck, trochanter and total body, respectively. In the smaller study (n=447), similar results were observed in women (6 to 36 months post-menopausal) treated with alendronic acid 5 mg daily for three years. In contrast, in both studies, women receiving placebo lost bone mass at a rate of approximately 1% per year. The longer term effects of alendronic acid in an osteoporosis prevention population are not known but clinical trial extensions of up to 10 years of continuous treatment are currently in progress.

Concomitant use with oestrogen/hormone replacement therapy (HRT)

The effects on BMD of treatment with alendronic acid 10 mg once-daily and conjugated oestrogen (0.625 mg/day) either alone or in combination were assessed in a two-year study of hysterectomised, post-menopausal, osteoporotic women. At two years, the increases in lumbar spine BMD from baseline were significantly greater with the combination (8.3%) than with either oestrogen or alendronic acid alone (both 6.0%).

The effects on BMD when alendronic acid was added to stable doses (for at least one year) of HRT (oestrogen \pm progestin) were assessed in a one-year study in post-menopausal, osteoporotic women. The addition of alendronic acid 10 mg once-daily to HRT produced, at one year, significantly greater increases in lumbar spine BMD (3.7%) vs. HRT alone (1.1%).

In these studies, significant increases or favourable trends in BMD for combined therapy compared with HRT alone were seen at the total hip, femoral neck and trochanter. No significant effect was seen for total body BMD.

Treatment of osteoporosis in men

The efficacy of alendronic acid 10 mg once daily in men (ages 31 to 87; mean, 63) with osteoporosis was demonstrated in a two-year study. At two years, the mean increases relative to placebo in BMD in men receiving alendronic acid 10 mg/day were: lumbar spine, 5.3%; femoral neck, 2.6%; trochanter, 3.1%; and total body, 1.6%. Alendronic acid was effective regardless of age, race, gonadal function, baseline rate of bone turnover, or baseline BMD. Consistent with much larger studies in post-menopausal women, in these men, alendronic acid 10 mg/day reduced the incidence of new vertebral fracture (assessed by quantitative radiography) relative to placebo (0.8% vs. 7.1%) and, correspondingly, also reduced height loss (-0.6 vs. -2.4mm).

Glucocorticoid-induced osteoporosis

The efficacy of alendronic acid 5 and 10 mg once-daily in men and women receiving at least 7.5 mg/day of prednisone (or equivalent) was demonstrated in two, one-year studies. At one year, the mean increases relative to placebo in BMD in patients receiving alendronic acid 5 mg/day from the combined studies were: lumbar spine, 2.4%; femoral neck, 2.2%; and trochanter, 1.6%. Total body BMD was maintained with this dose of alendronic acid. The increases in BMD with alendronic acid 10 mg/day were similar to those with alendronic acid 5 mg/day in all patients except for those post-menopausal women not receiving oestrogen therapy. In these women, the increases (relative to placebo) with alendronic acid 10 mg/day were greater than those with alendronic acid 5 mg/day at the lumbar spine (4.1% vs. 1.6%) and trochanter (2.8% vs. 1.7%), but not at other sites. Alendronic acid was effective regardless of dose or duration of glucocorticoid use.

The majority of patients from these studies who remained on at least 7.5 mg/day of prednisone or equivalent continued into a one-year extension. After two years of treatment, spine BMD increased by 3.7% and 5.0% relative to placebo with alendronic acid 5 and 10 mg/day respectively. Significant increases in BMD (relative to placebo) were also observed at the femoral neck, trochanter, and total body.

When the data from the three dosage groups (5 or 10 mg for two years or 2.5 mg for one year followed by 10 mg for one year) was pooled, there was a significant reduction in the incidence of patients with a new vertebral fracture at two years (alendronic acid, 0.7% vs placebo, 6.8%).

Paediatric patients:

Alendronate sodium has been studied in a small number of patients with osteogenesis imperfecta under the age of 18 years. Results are insufficient to support the use of alendronate sodium in paediatric patients with osteogenesis imperfecta.

IV.4 Clinical Efficacy

Alendronic acid (as sodium alendronate) is a well known active substance with established efficacy and tolerability.

Additional clinical efficacy studies are not necessary as this is a generic application and bioequivalence to the reference Fosamax has been shown.

IV.5 Clinical Safety

Alendronic acid (as sodium alendronate) is a well known active substance with established safety and tolerability.

Additional clinical safety studies are not necessary as this is a generic application and bioequivalence to the reference Fosamax has been shown.

Risk Management Plan is not necessary as this is a generic application.

PSUR cycle will be on a 3 yearly basis as per EU harmonised birth date.

The Marketing Authorisation Holder submitted a set of documents describing the Pharmacovigilance System, including information on the availability of an EU Qualified Person for Pharmacovigilance (EU-QPPV) and the means for notification of adverse reaction reports in the EU or from a Third Country.

IV.6 Discussion on the clinical aspects

As this is a generic formulation of the reference Fosamax, efficacy and safety is abridged to this reference medicine and additional efficacy or safety studies are unnecessary as bioequivalence has been shown.

Specific risk management plans are also unnecessary.

V OVERALL CONCLUSIONS

BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Alendronic Acid Aurobindo 10 mg tablets and Romax Once Weekly 70 mg tablets are generic forms of Fosamax 10mg tablet PA0035/083/001 and Fosamax once weekly 70mg tablet PA0035/083/003 MA holder Merck Sharpe & Dohme Limited.

The reference Fosamax is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the CHMP guidance documents. The SPC is consistent with that of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted, considered that demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation for Alendronic Acid Ceft 10 mg tablets and Alendronic Acid Ceft Once Weekly 70 mg tablets in 2011, these marketing authorisations were transferred to Milpharm Limited in 2012 and underwent a name change to Alendronic Acid Aurobindo 10 mg tablets and Romax Once Weekly 70 mg tablets.

VI REVISION DATE

March 2017

VII UPDATES**UPDATE**

This section reflects the significant changes following finalisation of the initial procedure.

Scope	Procedure number	Product Information affected	Date of start of procedure	Date of end of procedure	Approval/non approval
National Variation IB Foreseen B.II.f.1.B.1	PA1050/019/002	SPC Section 6.3	09/02/2017	15/03/2017	Approved
National Variation IB foreseen A.2.b	PA1050/019/002	PSD Section 1 SPC Section 1 SPC Section 4.2 SPC Section 4.4 SPC Section 5.1	07/01/2015	23/02/2015	Approved
National Variation IB B.II.e.I.a.1	PA1050/019/002	SPC Section 4.8 SPC Section 6.5	24/07/2014	07/10/2014	Approved
National Variation IB foreseen A.2.b	PA1050/019/002	PSD Section 1 PSD Section 2 SPC Section 4.1 SPC Section 4.2 SPC Section 4.3 SPC Section 4.6 SPC Section 4.8	30/04/2012	12/06/2012	Approved
National Transfer	PA1050/019/002	PSD Section 1 PSD Section 2 SPC Section 4.1 SPC Section 4.3 SPC Section 4.4 SPC Section 4.6 SPC Section 4.8 SPC Section 5.1 SPC Section 7 SPC Section 8	13/03/2012	13/07/2012	Approved