

ALENDRONIC ACID 70MG TABLETS

PL 15764/0032

UKPAR

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ALENDRONIC ACID 70MG TABLETS

PL 15764/0032

LAY SUMMARY

The MHRA today granted Strandhaven Limited a Marketing Authorisation (licence) for the medicinal product Alendronic Acid 70mg Tablets (PL 15764/0032). This is a prescription-only medicine (POM) for the treatment of Postmenopausal osteoporosis.

The active ingredient, alendronate monosodium trihydrate, belongs to a group of medicines called “bisphosphonates”. It works by preventing the loss of bone that occurs in women after they have been through the menopause, and helps to rebuild bone.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Alendronic acid 70mg Tablets outweigh the risks, hence a Marketing Authorisation has been granted.

ALENDRONIC ACID 70MG TABLETS

PL 15764/0032

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted a marketing authorisation for the medicinal product Alendronic acid 70mg Tablets (PL 15764/0032) on 26th October 2007. The product is a Prescription-only medicine.

This product is submitted as a hybrid application under Article 10.3 cross referring to Fosamax 5mg tablets authorised to Merck Sharp & Dohme Ltd, 23 June 1993.

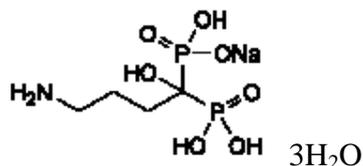
The active ingredient of Alendronic Acid 70 mg Tablets, alendronate monosodium trihydrate, is a bisphosphonate that inhibits osteoclastic bone resorption with no direct effect on bone formation.

The active ingredient is a potent inhibitor of osteoclast-mediated bone resorption. It is indicated for the treatment or prevention of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Alendronate monosodium trihydrate



Description: White or almost white crystalline powder

Solubility: Soluble in water

Chemical name: (4-amino-1-hydroxybutylidene)bisphosphonic acid monosodium salt trihydrate

Molecular formula: $C_4H_{12}NNaO_7P_2$

The active substance used in the manufacture of the final product is in compliance with GMP and letter of access to the Drug Master File has been provided.

An appropriate specification based on the European Pharmacopoeia has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Active alendronate sodium trihydrate is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data has been provided.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely crospovidone, cellulose microcrystalline and magnesium stearate.

All excipients used comply with their respective European Pharmacopoeial monograph. Satisfactory certificates of analysis have been provided for all excipients.

A satisfactory TSE declaration for magnesium stearate is provided.

There were no novel excipients used and no overages.

Dissolution and impurity profiles

Dissolution and impurity profiles for the drug product were found to be similar to that for the reference product.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches. The results are satisfactory.

Finished product specification

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System

Product is packaged in blisters composed of aluminium and PVC/PVDC packed in to a carton box. Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory. All primary product packaging complies with EU legislation regarding contact with food. The pack size is 4 tablets.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years when stored in the proposed blisters has been set. This is acceptable.

All results obtained were within specification.

Conclusion

It is recommended that a Marketing Authorisation is granted for this application.

The proposed product is considered to be a generic medicinal product to the reference product with respect to qualitative and quantitative content of the active substance, pharmaceutical form and bioequivalence.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are required for an application of this type.

CLINICAL ASSESSMENT

CLINICAL BACKGROUND

Alendronic acid is a potent inhibitor of osteoclast-mediated bone resorption. It is indicated for the treatment or prevention of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures.

The oral absorption of alendronic acid is limited under fasting conditions (<2%) and negligible in the presence of food. The ultimate site of sequestration is the bone, especially osteoclasts. Alendronate decreases bone turnover leading to progressive gains in bone mass. Alendronic acid is pharmacologically inactive when incorporated in bone matrix.

The active ingredient alendronic acid is a bisphosphonate that inhibits osteoclastic bone resorption with no direct effect on bone formation. Preclinical studies have shown preferential localization of alendronate to the sites of active resorption. Activity of the osteoclasts is inhibited, but recruitment or attachment of osteoclasts is not affected. The bone formed during treatment with alendronate is of normal quality.

Osteoporosis remains the leading cause of bone fracture and associated morbidity in postmenopausal women today. Basically osteoporosis is a loss of bone mass and its aetiology involves genetic, environmental, hormonal and nutritional factors.

Osteoporosis is defined as BMD of the spine or hip 2.5 SD below the mean value of a normal young population or as a previous fragility fracture, irrespective of BMD.

Alendronic acid has been available as a 5 mg tablet (Fosamax®, MSD) for daily treatment of osteoporosis. More recently, a once weekly 70 mg tablet of alendronate has become available, which retains all the therapeutic benefits of the lower dose tablet, but makes dosing and compliance issues far simpler for patients, since therapy is long-term.

Strandhaven Limited T/A Somex Pharma has now developed a generic 70 mg Alendronic Acid Tablet, which is intended to substitute for the originator product Fosamax® 70 mg (MSD) for the treatment of postmenopausal osteoporosis.

Since alendronate is rapidly taken-up by bone shortly after administration, plasma levels are below the level of quantification, thereby ruling-out a conventional bioequivalence study with measurement of plasma levels of the drug. It is also known that the mean terminal half-life of elimination of alendronate from bone was exceedingly long (estimated to be 10.9 years with a range of 5.4 - 19 years). This may potentially rule-out the conduct of crossover-type trials because of the possibility of significant urinary drug levels from the first dosing period being present when the subject returns for the second drug period. However, in practice it has been found that the maximum rates of primary urinary alendronate excretion occur between 1-3 hours after dosing and that over 90% of drug to be excreted renally is recovered in a 0-72 hour urine sampling period, giving a half-life based on urinary excretion data of 33 ± 19 hours. Furthermore, it was shown that the release of drug from bone is not a significant cause of carryover effects, thus permitting the use of crossover designs.

The bioequivalence study submitted with this application has therefore used urinary pharmacokinetic parameters of Alendronate.

INDICATIONS

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

Assessor's comment:

The proposed indication is in line with the brand leader.

DOSE AND DOSE REGIMEN

The proposed dosage and dose regimen stated in Section 4.2 Posology and method of administration is:

“The recommended dosage is one 70 mg tablet once weekly.

To permit adequate absorption of alendronate:

Alendronic Acid must be taken at least 30 minutes before the first food, beverage, or medicinal product of the day with plain water only. Other beverages (including mineral water), food and some medicinal products are likely to reduce the absorption of alendronate (see 4.5 'Interaction with other medicinal products and other forms of interaction').

To facilitate delivery to the stomach and thus reduce the potential for local and oesophageal irritation/adverse experiences (see 4.4 'Special warnings and precautions for use'):

- Alendronic Acid should only be swallowed upon arising for the day with a full glass of water (not less than 200 ml or 7 fl.oz.).
- Patients should not chew the tablet or allow the tablet to dissolve in their mouths because of a potential for oropharyngeal ulceration.
- Patients should not lie down until after their first food of the day which should be at least 30 minutes after taking the tablet.
- Patients should not lie down for at least 30 minutes after taking Alendronic Acid.
- Alendronic Acid should not be taken at bedtime or before arising for the day.

Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate (see 4.4 'Special warnings and precautions for use').

Use in the elderly: In clinical studies there was no age-related difference in the efficacy or safety profiles of alendronate. Therefore no dosage adjustment is necessary for the elderly.

Use in renal impairment: No dosage adjustment is necessary for patients with GFR greater than 35 ml/min. Alendronic Acid is not recommended for patients with renal impairment where GFR is less than 35 ml/min, due to lack of experience.

Use in children: Alendronate has not been studied in children and should not be given to them.

Alendronic Acid 70 mg Tablets has not been investigated in the treatment of glucocorticoid-induced osteoporosis”.

Assessor's comment:

The proposed dosage and dose regimen is in line with the brand leader

GCP ASPECTS

A satisfactory GCP statement was included in the study report.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS

BIOEQUIVALENCE

One single dose bioequivalence study, using urinary data, was submitted comparing the Alendronic Acid 70 mg test formulation and reference Fosamax 70 mg tablet.

Methods

This was a randomised, open-label, crossover, two-period design; in which a single oral dose of each formulation (test and reference) was administered.

A single oral dose of Alendronic Acid 70 mg was administered in each period of the study with 240 ml of drinking water after an overnight fast of at least 10 hours. In order to guarantee an adequate hydration and urinary excretion, subjects must increase water intake at least 1 hour prior to 3 hours after drug administration. Thereafter, until the end of the experimental session water intake was "ad libitum".

The washout period was greater than 14 days.

Urine samples were collected at 12 time intervals from each subject during each period. Samples were stored at -30°C until transfer to the analytical facility for assay of Alendronic Acid.

Test and reference products

Alendronic acid once weekly 70 mg tablets has been compared to Fosamax 70 mg tablets.

Population(s) studied

A total of 80 healthy adult, male and female (35/45) subjects (with no mention of ethnicity); aged 18-40 years were enrolled in the study. There were no dropout/withdrawal; therefore all 80 subjects completed the study.

Analytical methods

Urine samples were analyzed for Alendronic Acid using a validated LCMS method.

Statistical methods

Statistical analysis was performed using analysis of variance (ANOVA) model which includes the following factors: subject, formulation, period and administrations sequence. Multiplicative variables (Ae and Rmax) were transformed logarithmically (Ln).

Non-parametric analysis was carried out.

Ratio's of LSM, as well as 90% CI were determined. In the protocol it was stated that bioequivalence would be concluded when 90% CI were between 0.80-1.25 for LN Ae (T/R) and LN Rmax (T/R).

Results

Table 1: Main pharmacokinetic parameters

Parameter	Difference	Difference SE	Ratio (%Ref)	CI- 90 Lower	CI- 90 Upper
Ln (excreted quantity)	0.0346	0.0957	103.5	88.3	121.4
Ln (Rate max)	0.0435	0.0871	104.5	90.4	120.8
Ln (AUClast)	0.0252	0.0945	102.6	87.6	120.0
Ln (AUCinf)	0.0255	0.0937	102.6	87.8	119.9

**ln-transformed values*

Pharmacokinetic conclusion

Based on the submitted bioequivalence study Alendronic Acid 70 mg Tablet is considered bioequivalent with Fosamax 70 mg.

PHARMACODYNAMICS

N/A

CLINICAL EFFICACY

No new efficacy data were submitted by the applicant. The documented clinical efficacy of the active substance remains satisfactory for the proposed indications and dosages.

CLINICAL SAFETY

Safety findings in the bioequivalence study were those associated with the drug's use and were similar and of comparable magnitude between the two products. No new safety data were submitted with the application. The recorded safety profile of the active remains satisfactory when used in the proposed indications and at the recommended dosages.

EXPERT REPORTS

The expert report is written by a medically qualified pharmaceutical consultant and is satisfactory.

PRODUCT LITERATURE

SPC

Clinically satisfactory

PATIENT INFORMATION LEAFLET

This is satisfactory

LABEL

Clinically satisfactory

OVERALL CONCLUSION

The applicant has demonstrated bioequivalence. A marketing authorisation should be granted for this product.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Alendronic Acid 70mg Tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

Based on the submitted bioequivalence study Alendronic Acid 70 mg Tablet is considered bioequivalent with Fosamax 70 mg.

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory..

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's product and the innovator product are interchangeable. Extensive clinical experience with Alendronic Acid is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

ALENDRONIC ACID 70MG TABLETS**PL 15764/0032****STEPS TAKEN FOR ASSESMENT**

1	The MHRA received the marketing authorisation applications on 29 th March 2007
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 26 th April 2007
3	Following assessment of the applications the MHRA requested further information relating to the clinical dossiers on 10 th July 2007 quality dossiers on 5 th June 2007
4	The applicant responded to the MHRA's requests, providing further information to the quality sections on 23 rd August 2007 and 10 th July 2007 for the clinical sections
5	The applications were determined on 26 th October 2007

**ALENDRONATE SODIUM 70mg TABLETS
PL 15764/0032**

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS**1 NAME OF THE MEDICINAL PRODUCT**

Alendronic Acid 70 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains the equivalent of 70 mg of alendronic acid as 91.37 mg alendronate monosodium trihydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

White oval flat tablets, with dimensions of 14 x 8 mm and marked on one face with "70"

4 CLINICAL PARTICULARS**4.1 THERAPEUTIC INDICATIONS**

Treatment of postmenopausal osteoporosis. Sodium alendronate reduces the risk of vertebral and hip fractures.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

The recommended dosage is one 70 mg tablet once weekly.

To permit adequate absorption of alendronate:

Sodium alendronate must be taken at least 30 minutes before the first food, beverage, or medicinal product of the day with plain water only. Other beverages (including mineral water), food and some medicinal products are likely to reduce the absorption of alendronate (see 4.5 'Interaction with other medicinal products and other forms of interaction').

To facilitate delivery to the stomach and thus reduce the potential for local and oesophageal irritation/adverse experiences (see 4.4 'Special warnings and precautions for use'):

- Sodium alendronate should only be swallowed upon arising for the day with a full glass of water (not less than 200 ml or 7 fl.oz.).
- Patients should not chew the tablet or allow the tablet to dissolve in their mouths because of a potential for oropharyngeal ulceration.
- Patients should not lie down until after their first food of the day which should be at least 30 minutes after taking the tablet.
- Patients should not lie down for at least 30 minutes after taking Sodium alendronate.
- Sodium alendronate should not be taken at bedtime or before arising for the day.

Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate (see 4.4 'Special warnings and precautions for use').

Use in the elderly: In clinical studies there was no age-related difference in the efficacy or safety profiles of alendronate. Therefore no dosage adjustment is necessary for the elderly.

Use in renal impairment: No dosage adjustment is necessary for patients with GFR greater than 35 ml/min. Alendronate is not recommended for patients with renal impairment where GFR is less than 35 ml/min, due to lack of experience.

Use in children: Alendronate has not been studied in children and should not be given to them.

Sodium alendronate 70 mg Tablets has not been investigated in the treatment of glucocorticoid-induced osteoporosis.

4.3 CONTRAINDICATIONS

Abnormalities of the oesophagus and other factors which delay oesophageal emptying such as stricture or achalasia.

- Inability to stand or sit upright for at least 30 minutes.
- Hypersensitivity to alendronate or to any of the excipients.
- Hypocalcaemia.
- See also 4.4 'Special warnings and precautions for use'.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Alendronate can cause local irritation of the upper gastro-intestinal mucosa. Because there is a potential for worsening of the underlying disease, caution should be used when alendronate is given to patients with active upper gastro-intestinal problems, such as dysphagia, oesophageal disease, gastritis, duodenitis, ulcers, or with a recent history (within the previous year) of major gastro-intestinal disease such as peptic ulcer, or active gastro-intestinal bleeding, or surgery of the upper gastro-intestinal tract other than pyloroplasty (see 4.3 'Contra-indications').

Oesophageal reactions (sometimes severe and requiring hospitalisation), such as oesophagitis, oesophageal ulcers and oesophageal erosions, rarely followed by oesophageal stricture, have been reported in patients receiving alendronate. Physicians should therefore be alert to any signs or symptoms signalling a possible oesophageal reaction and patients should be instructed to discontinue alendronate and seek medical attention if they develop symptoms of oesophageal irritation such as dysphagia, pain on swallowing or retrosternal pain, new or worsening heartburn.

The risk of severe oesophageal adverse experiences appears to be greater in patients who fail to take alendronate properly and/or who continue to take alendronate after developing symptoms suggestive of oesophageal irritation. It is very important that the full dosing instructions are provided to, and understood by the patient (see 4.2 'Posology and method of administration'). Patients should be informed that failure to follow these instructions may increase their risk of oesophageal problems.

While no increased risk was observed in extensive clinical trials, there have been rare (post-marketing) reports of gastric and duodenal ulcers, some severe and with complications. A causal relationship cannot be ruled out.

Patients should be instructed that if they miss a dose of Sodium alendronate 70 mg, they should take one tablet on the morning after they remember. They should not take two tablets on the same day but should return to taking one tablet once a week, as originally scheduled on their chosen day.

Alendronate is not recommended for patients with renal impairment where GFR is less than 35 ml/min, (see 4.2 'Posology and method of administration').

Causes of osteoporosis other than oestrogen deficiency and ageing should be considered.

Hypocalcaemia must be corrected before initiating therapy with alendronate (see 4.3 'Contra-indications'). Other disorders affecting mineral metabolism (such as vitamin D deficiency and hypoparathyroidism) should also be effectively treated. In patients with these conditions, serum calcium and symptoms of hypocalcaemia should be monitored during therapy with Sodium alendronate.

Due to positive effects of alendronate in increasing bone mineral, decreases in serum calcium and phosphate may occur. These are usually small and asymptomatic. However, there have been reports of symptomatic hypocalcaemia, which occasionally have been severe and often occurred in patients with predisposing conditions (e.g. hypoparathyroidism, vitamin D deficiency and calcium malabsorption). Ensuring adequate calcium and vitamin D intake is therefore particularly important in patients receiving glucocorticoids.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

If taken at the same time, it is likely that food and beverages (including mineral water), calcium supplements, antacids, and some oral medicinal products will interfere with absorption of alendronate. Therefore, patients must wait at least 30 minutes after taking alendronate before taking any other oral medicinal product (see 4.2 'Posology and method of administration' and 5.2 'Pharmacokinetic properties').

No other interactions with medicinal products of clinical significance are anticipated. A number of patients in the clinical trials received oestrogen (intravaginal, transdermal, or oral) while taking alendronate. No adverse experiences attributable to their concomitant use were identified.

Although specific interaction studies were not performed, in clinical studies alendronate was used concomitantly with a wide range of commonly prescribed medicinal products without evidence of clinical adverse interactions.

4.6 PREGNANCY AND LACTATION

There are no adequate data from the use of alendronate monosodium trihydrate in pregnant women. Animal studies do not indicate direct harmful effects with respect to pregnancy, embryonal/foetal development, or postnatal development. Alendronate given during pregnancy in rats caused dystocia related to hypocalcemia (see 5.3 'Preclinical safety data'). Given the indication, alendronate should not be used during pregnancy.

It is not known whether alendronate is excreted into human breast milk. Given the indication, alendronate should not be used by breast-feeding women.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No effects on ability to drive and use machines have been observed.

4.8 UNDESIRABLE EFFECTS

In a one-year study in post-menopausal women with osteoporosis the overall safety profiles of 'Fosamax' Once Weekly 70 mg (n=519) and alendronate 10 mg/day (n=370) were similar.

In two three-year studies of virtually identical design, in post-menopausal women (alendronate 10 mg: n=196, placebo: n=397) the overall safety profiles of alendronate 10 mg/day and placebo were similar.

Adverse experiences reported by the investigators as possibly, probably or definitely drug-related are presented below if they occurred in $\geq 1\%$ in either treatment group in the one-year study, or in $\geq 1\%$ of patients treated with alendronate 10 mg/day and at a greater incidence than in patients given placebo in the three-year studies:

	One-Year Study		Three-Year Studies	
	'Fosamax' Once Weekly 70 mg (n = 519)	Alendronate 10 mg/day (n = 370)	Alendronate 10 mg/day (n = 196)	Placebo (n = 397)

	%	%	%	%
<i>Gastro-intestinal</i>				
abdominal pain	3.7	3.0	6.6	4.8
dyspepsia	2.7	2.2	3.6	3.5
acid regurgitation	1.9	2.4	2.0	4.3
Nausea	1.9	2.4	3.6	4.0
abdominal distention	1.0	1.4	1.0	0.8
constipation	0.8	1.6	3.1	1.8
diarrhoea	0.6	0.5	3.1	1.8
dysphagia	0.4	0.5	1.0	0.0
flatulence	0.4	1.6	2.6	0.5
Gastritis	0.2	1.1	0.5	1.3
gastric ulcer	0.0	1.1	0.0	0.0
oesophageal ulcer	0.0	0.0	1.5	0.0
<i>Musculoskeletal</i>				
musculoskeletal (bone, muscle or joint) pain	2.9	3.2	4.1	2.5
muscle cramp	0.2	1.1	0.0	1.0
<i>Neurological</i>				
headache	0.4	0.3	2.6	1.5

The following adverse experiences have also been reported during clinical studies and/or post-marketing use:

Common (≥ 1/100, <1/10)

Gastro-intestinal: abdominal pain, dyspepsia, constipation, diarrhoea, flatulence, oesophageal ulcer*, dysphagia*, abdominal distension, acid regurgitation.

Musculoskeletal: musculoskeletal (bone, muscle or joint) pain.

Neurological: headache.

Uncommon (≥ 1/1,000, <1/100)

Body as a whole: rash, pruritus, erythema

Gastro-intestinal: nausea, vomiting, gastritis, oesophagitis*, oesophageal erosions*, melaena.

Rare (≥ 1/10,000, <1/1,000)

Body as a whole: hypersensitivity reactions including urticaria and angioedema. Transient symptoms as in an acute-phase response (myalgia, malaise and rarely, fever), typically in association with initiation of treatment. Rash with photosensitivity. Symptomatic hypocalcaemia, often in association with predisposing conditions (see 4.4 'Special warnings and precautions for use').

Gastro-intestinal: oesophageal stricture*, oropharyngeal ulceration*, upper gastrointestinal PUBs (perforation, ulcers, bleeding), although a causal relationship cannot be ruled out.

Special senses: uveitis, scleritis, episcleritis.

Isolated cases of severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported.

* See 4.4 'Special warnings and precautions for use' and 4.2 'Posology and method of administration'.

Laboratory test findings

In clinical studies, asymptomatic, mild and transient decreases in serum calcium and phosphate were observed in approximately 18 and 10%, respectively, of patients taking alendronate 10 mg/day versus approximately 12 and 3% of those taking placebo. However, the incidences of decreases in serum calcium to <8.0 mg/dl (2.0 mmol/l) and serum phosphate to \leq 2.0 mg/dl (0.65 mmol/l) were similar in both treatment groups.

4.9 OVERDOSE

Hypocalcaemia, hypophosphataemia and upper gastro-intestinal adverse events, such as upset stomach, heartburn, oesophagitis, gastritis, or ulcer, may result from oral overdosage.

No specific information is available on the treatment of overdosage with alendronate. Milk or antacids should be given to bind alendronate. Owing to the risk of oesophageal irritation, vomiting should not be induced and the patient should remain fully upright.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Bisphosphonate, for the treatment of bone diseases.
ATC Code: M05B A04

The active ingredient of Sodium alendronate 70 mg Tablets, alendronate monosodium trihydrate, is a bisphosphonate that inhibits osteoclastic bone resorption with no direct effect on bone formation. Preclinical studies have shown preferential localisation of alendronate to sites of active resorption. Activity of osteoclasts is inhibited, but recruitment or attachment of osteoclasts is not affected. The bone formed during treatment with alendronate is of normal quality.

Treatment of post-menopausal osteoporosis

Osteoporosis is defined as BMD of the spine or hip 2.5 SD below the mean value of a normal young population or as a previous fragility fracture, irrespective of BMD.

The therapeutic equivalence of 'Fosamax' Once Weekly 70 mg (n=519) and alendronate 10 mg daily (n=370) was demonstrated in a one-year multicentre study of post-menopausal women with osteoporosis. The mean increases from baseline in lumbar spine BMD at one year were 5.1% (95% CI: 4.8, 5.4%) in the 70 mg once-weekly group and 5.4% (95% CI: 5.0, 5.8%) in the 10 mg daily group. The mean BMD increases were 2.3% and 2.9% at the femoral neck and 2.9% and 3.1% at the total hip in the 70 mg once weekly and 10 mg daily groups, respectively. The two treatment groups were also similar with regard to BMD increases at other skeletal sites.

The effects of alendronate 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 alendronate 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 (alendronate 3.2% vs placebo 6.2%) in the proportion of patients treated with alendronate 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 using alendronate daily (5 mg daily for two years and 10 mg daily for either one or two additional years):

- FIT 1: A three-year study of 2,027 patients who had at least one baseline vertebral (compression) fracture. In this study alendronate daily reduced the incidence of ≥ 1 new vertebral fracture by 47% (alendronate 7.9% vs. placebo 15.0%). In addition, a statistically significant reduction was found in the incidence of hip fractures (1.1% vs. 2.2%, a reduction of 51%).
- FIT 2: A four-year study of 4,432 patients with low bone mass but without a baseline vertebral fracture. In this study, a significant difference was observed in the analysis of the subgroup of osteoporotic women (37% of the global population who correspond with the above definition of osteoporosis) in the incidence of hip fractures (alendronate 1.0% vs. placebo 2.2%, a reduction of 56%) and in the incidence of ≥ 1 vertebral fracture (2.9% vs. 5.8%, a reduction of 50%).

5.2 PHARMACOKINETIC PROPERTIES

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%).

Distribution

Studies in rats show that alendronate transiently distributes to soft tissues following 1 mg/kg intravenous 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 intravenous dose of [14 C] 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 intravenous 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 six hours following intravenous 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 medicinal products 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 intravenous 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').

5.3 PRECLINICAL SAFETY DATA

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. Studies in rats have shown that treatment with alendronate during pregnancy was associated with dystocia in dams during parturition which was related to hypocalcaemia. In studies, rats given high doses showed an increased incidence of incomplete foetal ossification. The relevance to humans is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Microcrystalline cellulose
Crospovidone
Magnesium stearate

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

36 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

This medicinal product does not require any special storage conditions.

6.5 NATURE AND CONTENTS OF CONTAINER

Al/Al blisters

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Strandhaven Limited T/A Somex Pharma
600 High Road
Seven Kings
Ilford
Essex
IG3 IBS
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 15764/0032

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26/10/2007

10 DATE OF REVISION OF THE TEXT

26/10/2007

PACKAGE LEAFLET
ALENDRONIC ACID 70 MG TABLETS
(Alendronate monosodium trihydrate)

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this Leaflet

1. What Alendronic Acid 70 mg Tablets are and what they are used for
2. Before you take Alendronic Acid 70 mg Tablets
3. How to take Alendronic Acid 70 mg Tablets
4. Possible side effects
5. How to store Alendronic Acid 70 mg Tablets
6. Further Information

1. WHAT ALENDRONIC ACID 70 MG TABLETS ARE AND WHAT THEY ARE USED FOR

The active ingredient, alendronate monosodium trihydrate, belongs to a group of medicines called "bisphosphonates". It works by preventing the loss of bone that occurs in women after they have been through the menopause, and helps to rebuild bone. Alendronic Acid is used to treat the following condition:

- Postmenopausal osteoporosis.

2. BEFORE YOU TAKE ALENDRONIC ACID 70 MG TABLETS

If any of the following applies to you, speak to your doctor or pharmacist before you start taking Alendronic Acid 70 mg Tablets as they may not be suitable for you.

Do not take Alendronic Acid 70 mg Tablets:

- If you are allergic (hypersensitive) to alendronate monosodium trihydrate or any of the other ingredients of Alendronic Acid 70 mg Tablets.
- If you have certain disorders of the Oesophagus (the tube that connects your mouth with your stomach).
- If you are unable to stand or sit upright for at least 30 minutes.
- If your doctor has told you that you have low blood calcium.
- If you are or think you may be pregnant.
- If you are breast-feeding.

Take special care with Alendronic Acid 70 mg Tablets:

It is important to talk to your doctor if you have any of the following conditions:

- you suffer from kidney problems
- you have any allergies
- you have trouble swallowing or digestive problems

Taking other medicines:

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without prescription.

- After swallowing your tablet, wait at least 30 minutes before taking any other medication for the day. Alendronic Acid 70 mg Tablets are only effective if taken when your stomach is empty.

Taking Alendronic Acid 70 mg Tablets with food and drink:

Patients must wait at least 30 minutes after taking alendronate before taking any food or drink.

Pregnancy and breast-feeding:

Alendronic Acid 70 mg Tablets can not be used during pregnancy and if you are breast-feeding.

Driving and using machines:

Your medicine does not usually affect your ability to drive or operate machinery.

Other precautions you should take:

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE ALENDRONIC ACID 70 MG TABLETS

Your doctor has decided on the dose which is suited to you. The length of your course of treatment will depend on what condition you are suffering from. Always take Alendronic Acid 70 mg Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

You may have previously been prescribed a 10 mg tablet of alendronate which is taken once a day. One Alendronic Acid 70 mg Tablet is taken once a week.

It is very important that you follow actions 2, 3, 4 and 5 described below. This will help the Alendronic Acid 70 mg Tablet reach your stomach quickly and help reduce the risk of irritating your oesophagus.

1. Choose the day of the week that best fits your schedule. Every week, take your Alendronic Acid 70 mg Tablet on your chosen day.

2. After getting up for the day and before taking your first food, drink or other medication, swallow your Alendronic Acid 70 mg Tablet with a full glass of plain water only (not less than 200ml or 7fl.oz.).

Do not chew or allow the tablet to dissolve in your mouth.

3. After swallowing your Alendronic Acid 70mg Tablet do not lie down - stay fully upright (or sat upright) for at least 30 minutes and do not lie down until after your first food of the day

4. Do not take Alendronic Acid 70 mg Tablets at bedtime or before getting up for the day.

5. If you develop difficulty or pain swallowing, chest pain, or new or worsening heartburn, stop taking Alendronic Acid 70 mg Tablets and contact your doctor.

6. After swallowing your Alendronic Acid 70 mg Tablet, wait at least 30 minutes before taking your first food, drink or other medication of the day, including antacids, calcium supplements and vitamins. Alendronic Acid 70 mg Tablets are only effective if taken when your stomach is empty.

If you take more Alendronic Acid 70 mg Tablets than you should:

If you (or someone else) accidentally take too many Alendronic Acid 70 mg Tablets, drink a full glass of milk and contact your doctor or pharmacist immediately.

If you forget to take Alendronic Acid 70 mg Tablets:

If you forget to take a dose, take one Alendronic Acid 70 mg Tablet on the morning after you remember. Do not take a double dose to make up for forgotten individual doses.

If you stop taking Alendronic Acid 70 mg Tablets:

Always contact your doctor or pharmacist before you stop taking Alendronic Acid 70 mg Tablets. Alendronic Acid 70 mg Tablets can treat your osteoporosis only if you continue to take the tablets.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Alendronic Acid 70 mg Tablets can cause side effects, although not everybody gets them. These are usually mild but some patients may experience digestive disturbances which may be severe.

If the following happens, stop taking the tablets and tell your doctor immediately or go to the accident and emergency department at your nearest hospital:

- An allergic reaction (angioedema): swelling of the face, lips, tongue or throat, or difficulty breathing or swallowing.

This is a very serious but rare side effect. You may need urgent medical attention or hospitalisation.

Side effects sometimes seen are:

Common - more than one in a hundred people but less than one in ten:

Gastro-intestinal: stomach pain, constipation, diarrhea, flatulence, oesophageal ulcer, acid regurgitation, swollen abdomen, swallowing difficulties, digestive problems.

Musculoskeletal: bone, muscle or joint pain.

Neurological: headache

Uncommon - more than one in a thousand people but less than one in a hundred:

Body as a whole: rash, reddening of the skin, itching.

Gastro-intestinal: feeling sick, being sick, swelling of the stomach wall, black or bloody stools, inflammation of the food passage, wearing away of the food passage.

Rare - more than one in ten thousand people but less than one in a thousand:

Body as a whole: allergic reaction including hives and swelling of the lips, tongue and throat, fever, discomfort, muscle pains, rash (occasionally made worse by sunlight), reduced blood calcium levels.

Gastro-intestinal: difficulty in swallowing, ulcers of the mouth, stomach and other peptic ulcers (some with bleeding).

Special senses: eye pain, diminished or hazy vision and/or seeing black floating spots.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE ALENDRONIC ACID 70 MG TABLETS

Keep out of the reach and sight of children.

This medicinal product does not require any special storage conditions.

Do not use Alendronic Acid 70 mg Tablets after the expiry date which is stated on the outer packaging. The expiry date refers to the last day of the month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Alendronic Acid 70 mg Tablets contain

- The active substance is alendronate monosodium trihydrate and each tablet contains 70 mg of alendronate monosodium trihydrate.
- The other ingredients are microcrystalline cellulose, crospovidone and magnesium stearate.

What Alendronic Acid 70 mg Tablets look like and contents of the pack

Each tablet is white, oval, flat and marked with a "70" on one side.

Alendronic Acid 70 mg Tablets are available in blisters of 4 tablets.

Marketing Authorisation Holder:

Somex Pharma, Seven Kings Ilford, Essex IG3 8BS
Manufacturer: Laboratorios Belmac S.A., Poligono Industrial Malpica, calle C, 50016- Zaragoza, Spain.

This leaflet was last updated in June 2006

ALENDRONIC ACID 70 mg Tablets

WEEK 1 WEEK 2

ALENDRONIC ACID 70 mg Tablets
(Alendronate monosodium trihydrate)

Somex Pharma
PL 15764/0032

WEEK 3 POM WEEK 4

ALENDRONIC ACID 70 mg Tablets

↑
BN

↑
EXPIRY