

**ALENDRONIC ACID 70MG TABLETS
PL 15922/0087-9**

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TABLE OF CONTENTS

Lay Summary	Page 2
Scientific discussion	Page 3
Steps taken for assessment	Page 13
Steps taken after authorisation – summary	Page 14
Summary of Product Characteristics	Page 15
Patient Information Leaflet	Page 25
Labelling	Page 30

**ALENDRONIC ACID 70MG TABLETS
PL 15922/0087-9**

LAY SUMMARY

The MHRA granted Apotex Europe Ltd Marketing Authorisations (licences) for the medicinal product Alendronic Acid 70mg Tablets (PL 15922/0087-9). This is a prescription only medicine (POM) for the prevention of bone loss (osteoporosis) that occurs in women after they have been through the menopause and for the reduction of the risk of spine and hip fractures.

Alendronic Acid 70mg Tablets contain the active ingredient alendronic acid which belongs to a group of non-hormonal medicines called bisphosphonates.

The test product was considered to be equivalent to the original product Fosamax Once Weekly 70mg Tablets (Merck Sharp & Dohme Ltd) based on the data submitted.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Alendronic Acid 70mg Tablets outweigh the risks, hence Marketing Authorisations have been granted.

**ALENDRONIC ACID 70MG TABLETS
PL 15922/0087-9**

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction	Page 4
Pharmaceutical assessment	Page 5
Preclinical assessment	Page 8
Clinical assessment (including statistical assessment)	Page 9
Overall conclusion and risk benefit assessment	Page 12

INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted Marketing Authorisations for the medicinal product Alendronic Acid 70mg Tablets to Apotex Europe Ltd on 26 February 2008. The product is a prescription only medicine.

A single strength of alendronic acid was submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC, claiming to be a generic product of Fosamax Once Weekly 70mg Tablets (Merck Sharp &Dohme Ltd). The reference product has been authorised in the UK since November 2000 which was a submitted as a line extension of Fosamax 10mg Tablets (Merck Sharp &Dohme Ltd) which was authorised in July 1995 and so the 10-year period of data exclusivity has expired.

The product contains the active ingredient alendronic acid and is indicated for the treatment of postmenopausal osteoporosis. It also reduces the risk of vertebral and hip fractures.

Alendronic acid (as sodium alendronate trihydrate) is a potent bisphosphonate which inhibits osteoclastic bone resorption.

All applications were submitted at the same time and depend on the bioequivalence study that compares the applicant's product with the reference product Fosamax Once Weekly 70mg Tablets (Merck Sharp & Dohme Ltd). Consequently, all sections of the Scientific Discussion refer to all applications.

PHARMACEUTICAL ASSESSMENT

COMPOSITION

The product is formulated as a tablet containing 70mg of the active pharmaceutical ingredient alendronic acid, as sodium alendronate trihydrate. The excipients present are magnesium stearate, mannitol powder and microcrystalline cellulose (PH 102).

Alendronic Acid 70mg Tablets are presented in clear PVC/PVDC/Al blisters in packs of 2, 4, 8, 12 and 40 tablets.

DRUG SUBSTANCE

Sodium alendronate trihydrate

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification based on the European Pharmacopoeia monograph is provided for sodium alendronate trihydrate.

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

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

Sodium alendronate trihydrate is stored in appropriate packaging.

Stability data have been generated supporting a retest period of 5 years when stored in the proposed packaging at room temperature.

DRUG PRODUCT

Other ingredients

All excipients used in the manufacture of the tablets are routinely tested for compliance with current relevant international standards.

Satisfactory certificates of analysis have been provided for all excipients.

Magnesium stearate is the only excipient used that contains material of animal or human origin. A Transmissible Spongiform Encephalopathies (TSE) Certificate has been provided for magnesium stearate confirming that the risk of transmitting TSEs is sufficiently low.

Dissolution profiles

Dissolution profiles for the drug product (Alendronic Acid 70mg Tablets) were found to be similar to the reference product (Fosamax Once Weekly 70mg Tablets) and are essentially pH independent. Due to the high solubility of the drug substance, it is considered that there will not be a bioavailability problem.

Impurity profiles

Comparative impurity data were generated on the drug product and the reference product (Fosamax Once Weekly 70mg Tablets). The profiles were similar, phosphate and phosphite levels were less than 0.05%, and the levels of aminobutanoic acid, unknown impurities and total impurities were comparable and low.

Manufacture

A full description and a detailed flow-chart of the manufacturing method including in-process control steps 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 of both strengths. The results are satisfactory.

Finished product specification

The proposed finished product specification is acceptable and the analytical methods used have been suitably validated. Batch analysis data have demonstrated compliance with the proposed release specification. Suitable reference standards were used.

Container closure system

Satisfactory specifications and certificates of analysis have been provided for the packaging components. All primary product packaging complies with EU legislation regarding contact with food.

Stability

Finished product stability data support the proposed shelf-life of 36 months with no special storage conditions.

Bioequivalence/bioavailability

Refer to the clinical assessment report.

SPC, PIL and Labels

The SPC and labels are pharmaceutically acceptable.

A patient information leaflet (PIL) has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act on the information that it contains.

CONCLUSION

The proposed product has been shown to be a generic product of the reference product and has met the requirements with respect to qualitative and quantitative content of the active substance. Similar dissolution profiles have been demonstrated for the proposed and reference products.

It is recommended that Marketing Authorisations should be granted for these applications.

PRECLINICAL ASSESSMENT

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

CLINICAL ASSESSMENT

INTRODUCTION AND BACKGROUND

These are generic abridged applications for tablets containing 70mg alendronic acid.

The applications are submitted under the provisions of Directive 2001/83/EC Article 10.1, claiming that Alendronic Acid 70mg Tablets are generic products of Fosamax Once Weekly 70mg Tablets (Merck Sharp & Dohme Ltd) which were authorised in the UK in November 2000.

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. Osteoporosis is essentially a loss of bone mass and its cause involves genetic, environmental, hormonal and nutritional factors.

INDICATIONS

The following indications have been approved:

Treatment of postmenopausal osteoporosis. Alendronic Acid 70 mg Tablets reduce the risk of vertebral and hip fractures.

DOSE AND DOSE SCHEDULE

The proposed dose and dose schedule for this product to be used for the above indications are consistent with those of the reference product.

CLINICAL PHARMACOLOGY

Since alendronic acid 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 alendronic acid 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 $33 \pm$

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.

A single centre, single dose, randomised, double-blind, two way crossover study was conducted in healthy male volunteers under fasted conditions. The study enrolled 150 volunteers of which 128 met the inclusion criteria, there were 16 dropouts giving 112 subjects being included in the full statistical analysis.

The test product used was Alendronic Acid 70mg Tablets and the reference product was Fosamax Once Weekly 70mg Tablets (Merck Sharp & Dohme Ltd), sourced from the UK.

Samples were taken from two hours prior to dosing up to 72 hours post dosing. The washout period was 14 days.

Results:

Parameter	Test product (Alendronate) Mean & C.V.	Reference (Fosamax) Mean& C.V.
$A_{e,72}$ (ng)	413354.1 (82.0)	425386.0 (83.5)
$\ln(A_{e,72})$ (ng)	12.6484 (6.1)	12.7102 (5.5)
AUC_{72} (ng)	415597.4 (83.0)	427222.5 (85.6)
$\ln(AUR_{72})$ (ng)	12.6477 (6.2)	12.7122 (5.5)
R_{max} (ng/h)	111231.4 (81.8)	117808.5 (80.3)
$\ln(R_{max})$ (ng/h)	11.3552 (6.4)	11.4388 (5.9)
T_{max} (h)*	1.5 (41.9)	1.5 (38.0)

*the median is presented and the statistical analysis is based on ranks.

Bioequivalence has been proposed on the basis of the maximum excretion rate (R_{max}) and amount of drug excreted unchanged in the urine over the entire period of sample collection (0-72 hours) (A_{e0-72}) of the test to reference formulation. The proposed target was 80% to 125% for the 90% confidence intervals. The results showed that the 90% CI for the ratios of mean A_{e72} , AUR_{72} and R_{max} for the test and reference formulations are all contained within 80% to 125%.

On the basis of this data the test Alendronic Acid 70mg Tablets and Fosamax Once Weekly 70mg Tablets are considered bioequivalent and equally well tolerated since the adverse events reported are in keeping with the known profile of the active substance.

CLINICAL EFFICACY

No new efficacy data are presented in these applications and none are required. The documented clinical efficacy of the active substance remains satisfactory for the proposed indications and dosages.

CLINICAL SAFETY

No new formal safety data are presented in these applications and none are required. The recorded safety profile of the active remains satisfactory when used in the proposed indications and at the recommended dosages.

CLINICAL EXPERT REPORT

The clinical expert report has been written by an appropriately qualified medical doctor. It is an adequate summary of the clinical data provided in the dossier.

SPC, PIL and LABELS

The SPC, PIL and labels are acceptable.

CONCLUSIONS

The clinical efficacy and safety of alendronic acid is well known from its extensive use in clinical practice. No new data were submitted and this is acceptable. Bioequivalence of the product has been shown. Marketing Authorisations should be granted for these applications.

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

Bioequivalence has been demonstrated between the applicant's Alendronic Acid 70mg Tablets and Fosamax Once Weekly 70mg Tablets (Merck Sharp & Dohme).

No new or unexpected safety concerns arose from these applications.

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 reference product are interchangeable. The risk benefit is, therefore, considered to be positive.

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STEPS TAKEN FOR ASSESSMENT

- 1 The MHRA received the Marketing Authorisation applications on 31 March 2005.
- 2 Following standard checks and communication with the applicant, the MHRA considered the applications valid on 15 April 2005.
- 3 Following assessment of the applications, the MHRA requested further information relating to the quality dossiers on 02 September 2005, 31 March 2006 and 21 March 2007 and further information relating to the clinical dossiers on 14 July 2006.
- 4 The applicant responded to the MHRA's requests, providing further information on 22 February 2006, 29 August 2006 and 06 June 2007 for the quality sections, and again on 21 October 2006 for the clinical sections.
- 5 The applications were determined on 26 February 2008.

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STEPS TAKEN AFTER AUTHORISATION – SUMMARY

Date submitted	Application type	Scope	Outcome
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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Alendronic Acid 70 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 70 mg alendronic acid (as alendronate sodium trihydrate).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

White, oval biconvex tablet, engraved "APO" on one side and "ALE 70" on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of postmenopausal osteoporosis. Alendronic Acid 70 mg Tablets reduce the risk of vertebral and hip fractures.

4.2 Posology and method of administration

For oral administration.

The recommended dosage is one 70 mg tablet once weekly.

To permit adequate absorption of alendronate:

Alendronic Acid 70 mg Tablets 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 70 mg Tablets 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 70 mg Tablets

- Alendronic Acid 70 mg Tablets 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 70 mg Tablets are not recommended for patients with renal impairment where GFR is less than 35 ml/min, due to lack of experience.

Use in children: Alendronic Acid 70 mg Tablets have not been studied in children and should not be given to them.

Alendronic Acid 70 mg Tablets have 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 Alendronic Acid 70 mg Tablets, 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 Alendronate Sodium.

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.

Osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection (including osteomyelitis) has been reported in patients with cancer receiving treatment regimens including primarily intravenously administered bisphosphonates. Many of these patients were also receiving chemotherapy with corticosteroids. Osteonecrosis of the jaw has also been reported in patients with osteoporosis receiving oral bisphosphonates.

A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, chemotherapy, radiotherapy, corticosteroids, poor oral hygiene).

While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop osteonecrosis of the jaw while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patient requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis in the jaw.

Clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

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

Use during pregnancy

There are no adequate data from the use of alendronate 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.

Use during lactation.

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

Not relevant.

4.8 Undesirable effects

In a one-year study in post-menopausal women with osteoporosis the overall safety profiles of Alendronate Sodium 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	
	Alendronate 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 and ranked under the following frequency:

- Very common: (>1/10)
Common: (>1/100, <1/10)
Uncommon: (>1/1,000, <1/100)
Rare: (>1/10,000, <1/1,000)
Very rare: (<1/10,000), including isolated reports.

Common ($\geq 1/100$, <1/10)

Nervous system disorders: headache.

Gastrointestinal disorders: abdominal pain, dyspepsia, constipation, diarrhoea, flatulence, oesophageal ulcer*, dysphagia*, abdominal distension, acid regurgitation.

Musculoskeletal, connective tissue and bone disorders: musculoskeletal (bone, muscle or joint) pain.

Uncommon ($\geq 1/1,000$, <1/100)

Gastrointestinal disorders: nausea, vomiting, gastritis, oesophagitis*, oesophageal erosions*, melaena.

Skin and subcutaneous tissue disorders: rash, pruritus, erythema

Rare ($\geq 1/10,000$, <1/1,000)

Immune system disorders: hypersensitivity reactions including urticaria and angioedema.

Metabolism and nutrition disorders: Symptomatic hypocalcaemia, often in association with predisposing conditions (see 4.4 'Special warnings and precautions for use').

Eye disorders: uveitis, scleritis.

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

Skin and subcutaneous tissue disorders: rash with photosensitivity.

Musculoskeletal, connective tissue and bone disorders: Osteonecrosis of the jaw has been reported in patients treated by bisphosphonates. The majority of the reports refer to cancer patients, but such cases have also been reported in patients treated for osteoporosis. Osteonecrosis of the jaw is generally associated with tooth extraction and/or local infection (including osteomyelitis). Diagnosis of cancer, chemotherapy, radiotherapy, corticosteroids and poor oral hygiene are also deemed as risk factors (see section 4.4).

General disorders and administrative site conditions: transient symptoms as in an acute-phase response (myalgia, malaise and rarely, fever), typically in association with initiation of treatment.

Very rare (<1/10,000) and isolated cases

Skin and subcutaneous tissue disorders: 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 alendronic acid (as alendronate sodium 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 alendronate sodium 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 [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 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

magnesium stearate

mannitol powder

microcrystalline cellulose (PH 102)

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

Clear PVC/PVDC/Al blisters containing 2 or 4 tablets.

Pack sizes: 2, 4, 8, 12, 40 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Apotex Europe Limited

Rowan House

41 London Street

Reading

Berkshire

RG1 4PS

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 15922/0087

PL 15922/0088

PL 15922/0089

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26/02/2008

10 DATE OF REVISION OF THE TEXT

26/02/2008

11 DOSIMETRY (IF APPLICABLE)

**12 INSTRUCTIONS FOR PREPARATION OF
RADIOPHARMACEUTICALS (IF APPLICABLE)**

PATIENT INFORMATION LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Alendronic Acid 70 mg Tablets

Alendronic acid (as alendronate sodium 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 pharmacist.
- This medicine has been prescribed for you. Do 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

Alendronic acid belongs to a group of non-hormonal medicines called bisphosphonates.

Alendronic Acid 70 mg Tablets are used to:

- prevent the loss of bone (osteoporosis) that occurs in women after they have been through the menopause
- reduce the risk of spine and hip fractures.

About osteoporosis

At the menopause the female body stops making oestrogen, which can result in bone loss and weakening (osteoporosis).

Initially, osteoporosis may have no obvious symptoms. However, if left untreated it can result in fractures (broken bones) occurring as a result of normal, everyday activities and instances which might not normally cause a fracture. Common fractures include: hip, spine, or wrist and can lead not only to pain but also to considerable deformity and disability (such as height loss, stooped posture, or 'dowager's hump', and loss of mobility).

Alendronic Acid 70 mg Tablets not only prevent the loss of bone that occurs in women after the menopause but actually helps to rebuild bone and reduces the risk of spine and hip fractures.

In addition to your treatment with Alendronic Acid 70 mg Tablets, your doctor may recommend that you make some lifestyle changes to help your condition. These are:

- Stop smoking: Smoking may increase the rate at which you lose bone and, therefore, may increase your risk of fracture.
- Take exercise: Bones need exercise to stay strong and healthy. Consult your doctor before you begin any exercise programme.
- Eat a balanced diet: Your doctor can advise you about your diet or whether you should take any dietary supplements.

2. Before you take Alendronic Acid 70 mg Tablets

Do not take Alendronic Acid 70 mg Tablets if:

- you are allergic (hypersensitive) to alendronic acid or any of the ingredients of Alendronic Acid 70 mg Tablets (see Section 6: Further Information)
- you have certain disorders of the oesophagus (the feeding tube that connects your mouth with your stomach)
- you are unable to stand or sit upright for at least 30 minutes
- your doctor has told you that you have low blood calcium.

If any of these apply to you, do not take Alendronic Acid 70 mg Tablets. Talk to your doctor first and follow the advice given.

Take special care with Alendronic Acid 70 mg Tablets

Talk to your doctor before taking Alendronic Acid 70 mg Tablets if:

- you suffer from kidney problems
- you have any swallowing or digestive problems
- you have gum disease
- you have a planned dental extraction.

A dental examination should be considered before you start treatment with Alendronic Acid 70 mg Tablets if you have any of the following conditions:

- you have cancer
- you are undergoing chemotherapy or radiotherapy
- you are taking corticosteroids
- you do not receive routine dental care
- you have gum disease.

Appropriate preventative dental care, as recommended by the dentist, should be followed during treatment.

Taking other medicines

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

If taken at the same time, other medicines which are taken by mouth (including antacids and calcium supplements) can have an effect on alendronic acid. Therefore, you must wait at least 30 minutes after taking alendronic acid before taking any other medicines which are taken by mouth (see Section 3: How to take Alendronic Acid 70 mg Tablets).

Taking Alendronic Acid 70 mg Tablets with food and drink

If taken at the same time, food and drink (including mineral water) can have an effect on alendronic acid. Alendronic acid is effective only if taken when your stomach is empty. Therefore, you must wait at least 30 minutes after taking Alendronic Acid 70 mg Tablets before taking food or drink.

Pregnancy and breast-feeding

You should not take alendronic acid if you:

- are pregnant, planning to become pregnant or if you think you may be pregnant
- are breast-feeding.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Alendronic Acid 70 mg Tablets should not affect your ability to drive or operate machinery.

Children

Alendronic Acid 70 mg Tablets should not be given to children.

3. How to take Alendronic Acid 70 mg Tablets

Alendronic Acid 70 mg Tablets are for oral use.

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 alendronic acid which is taken once a day, however, the usual dose of Alendronic Acid 70 mg Tablets is one 70 mg tablet **once weekly**.

It is very important that you follow the steps listed below to help the Alendronic Acid 70 mg Tablet reach your stomach quickly, help reduce potential for irritation of your oesophagus and to help make sure you benefit from Alendronic Acid 70 mg Tablets.

1. Choose the day of the week that best fits your schedule. Every week, take one Alendronic Acid 70 mg Tablet on your chosen day.
2. After getting up for the day and at least 30 minutes before taking your first food, drink, or other medicines (including antacids and calcium supplements), swallow your Alendronic Acid 70 mg Tablet with a full glass of **plain tap water** only (not less than 200 ml or 7 fl. oz.). Alendronic Acid 70 mg Tablets are effective only if taken when your stomach is empty. Do **not** take the tablet with:
 - mineral water
 - coffee or tea
 - juice.**Do not chew or allow your Alendronic Acid Tablet to dissolve in your mouth.**
3. After swallowing your Alendronic Acid 70 mg Tablet **do not lie down**. Stay fully upright (sitting, standing or walking) 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.**

If patients do not drink a full glass of water with their Alendronic Acid 70 mg Tablet and/or if they lie down within 30 minutes after taking their tablet or before their first food of the day, the following reactions may occur: irritation or ulceration of the oesophagus (the feeding tube that connects your mouth with your stomach) which can cause chest pain, heartburn, difficulty or pain upon swallowing and/or scarring leading to narrowing of the oesophagus.
If you develop difficulty or pain upon swallowing, chest pain, or new or worsening heartburn, stop taking Alendronic Acid 70 mg Tablets and contact your doctor.

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

If you take too many tablets by mistake, drink a full glass of milk and contact your doctor immediately. Do not make yourself vomit, and do not lie down.

If you forget to take Alendronic Acid 70 mg Tablets

If you miss a dose, take one Alendronic Acid 70 mg Tablet the morning after you remember. Do not take two tablets on the same day. Return to taking one tablet once a week, as originally scheduled on your chosen day. Do not take a double dose to make up for a forgotten tablet.

If you stop taking Alendronic Acid 70 mg Tablets

It is important that you continue taking Alendronic Acid 70 mg Tablets for as long as your doctor prescribes the medicine. 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

Most patients do not experience any side effects from taking Alendronic Acid 70 mg Tablets. However, like all medicines, Alendronic Acid 70 mg Tablets can cause side effects, although not everybody gets them.

Common (affecting more than 1 person in 100, but less than 1 in 10)

- headache
- abdominal pain, indigestion, constipation, diarrhoea, flatulence, full or bloated feeling in the stomach, acid reflux
- difficulty swallowing, ulceration of the oesophagus which can cause chest pain, heartburn or difficulty or pain when swallowing
- bone, muscle or joint pain.

Uncommon (affecting more than 1 person in 1,000, but less than 1 in 100)

- nausea, vomiting, black or bloody stools
- irritation or inflammation of the stomach or oesophagus
- rash, itching (pruritus), reddening of the skin (erythema).

Rare (affecting more than 1 person in 10,000, but less than 1 in 1,000)

- eye pain, reduced or hazy vision and/or black floating spots
- narrowing of the oesophagus
- mouth ulcers (when the tablets have been chewed or sucked)
- stomach or peptic ulcers (sometimes severe or with bleeding) although it is not known whether or not these were caused by treatment with Alendronic Acid 70 mg Tablets
- jaw problems associated with delayed healing and infection, often following tooth extraction (see "Take special care with Alendronic Acid 70 mg Tablets" in Section 2)
- allergic reactions such as hives or rarely, swelling of the face, lips, tongue and/or throat possibly causing difficulty in breathing or swallowing (angioedema)
- transient flu-like symptoms, such as aching muscles, generally feeling unwell and sometimes with fever, usually at the start of treatment
- rash made worse by sunlight
- symptoms of low blood calcium levels including muscle cramps or spasms and/or tingling sensation in the fingers or around the mouth.

Very rare (affecting less than 1 person in 10,000, including isolated reports)

- severe skin reactions including Stevens-Johnson syndrome (severe allergic reaction that can result in skin blistering, fever and eye damage) and toxic epidermal necrolysis (skin becomes intensely red and peels off in the manner of a second degree burn, often accompanied by blisters).

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.

Use-by date

Do not use Alendronic Acid 70 mg Tablets after the expiry date which is stated on the carton and blister after "EXP". The expiry date refers to the last day of that 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 contains**

- The active substance is alendronic acid (as alendronate sodium trihydrate). Each tablet contains 70 mg alendronic acid.
- The other ingredients are: magnesium stearate, mannitol powder and microcrystalline cellulose (PH 102).

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

Alendronic Acid 70 mg Tablets are white, oval biconvex tablets, marked with "APO" on one side and "ALE 70" on the other side.

Alendronic Acid 70 mg Tablets are supplied in blister packs containing 2 or 4 tablets packed in a carton together with a patient leaflet. Pack sizes consists of 2, 4, 8, 12, or 40 tablets. Not all pack sizes may be available.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:

Apotex Europe Ltd, Rowan House, 41 London Street, Reading, Berkshire, RG1 4PS, United Kingdom

Manufacturer:

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Distributor:

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LABELLING





