

**ALENDRONIC ACID 70MG TABLETS
PL 16002/0075**

UKPAR

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**ALENDRONIC ACID 70 MG TABLETS
PL 16002/0075**

LAY SUMMARY

The MHRA granted Pharmafile Limited a Marketing Authorisation (licence) for the medicinal product Alendronic Acid 70 mg Tablets (PL 16002/0075). This is a prescription-only medicine (POM) for the treatment of postmenopausal osteoporosis.

Alendronic Acid 70 mg Tablets contain the active ingredient, alendronate sodium trihydrate. Following menopause, the cells that break down the bone (osteoclasts) may become more active than those that stimulate the manufacture of new bone (osteoblasts) and, as a result, loss of bone density and osteoporosis can occur. Alendronate sodium trihydrate can restore the osteoclast-to-osteoblast balance by blocking osteoclasts, thus preventing loss of bone mass and helping to rebuild lost bone.

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

The licence for this product was subsequently cancelled on 13th December 2007.

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 70 mg Tablets (PL 16002/0075) on 19th March 2007. The product is a prescription-only medicine.

This application was submitted according to Article 10(1) of EC Directive 2001/83, as amended, a generic product of Fosamax[®] Once Weekly 70 mg Tablets (PL 00025/0399), authorised to Merck Sharp & Dohme Limited on 10th November 2000.

The product contains the active ingredient alendronate sodium trihydrate, a bisphosphonate that is a potent inhibitor of osteoclast-mediated bone resorption. These tablets are indicated for the treatment or prevention of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures.

The licence for this product was subsequently cancelled on 13th December 2007.

PHARMACEUTICAL ASSESSMENT

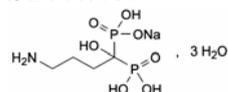
DRUG SUBSTANCE

Sodium alendronate trihydrate

INN: Sodium alendronate trihydrate

Chemical Name: 4-amino-1-hydroxybutylidene bisphosphonic acid monosodium salt trihydrate

Structure:



Molecular formula: C₄H₁₂NNaO₇P₂, 3H₂O

Molecular weight: 325.1

Physical form: White to almost white crystalline powder

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 specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

The structure has been confirmed by IR, NMR and MS.

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.

The active substance is packed in to low density polyethylene bags and placed in a fibre drum. The material is double bagged and sealed with a plastic clamp. 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 have been generated supporting a retest period of 24 months, with no specific storage instructions.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely croscarmellose sodium, colloidal anhydrous silica, magnesium stearate and cellactose 80.

All excipients used comply with their respective European Pharmacopoeial monograph, with the exception of cellactose 80 which complies with an in-house specification. Satisfactory certificates of analysis have been provided for all excipients.

None of the excipients used contain material of animal or human origin. 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 those 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 three batches of Alendronate 70mg tablets and 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 white opaque polyvinyl chloride (PVC). 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 product is packaged in sizes of 2, 4 or 12 tablets.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years has been set, which is satisfactory. There are no specific storage conditions and this is acceptable on the basis of the data presented.

Conclusion

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

PRECLINICAL ASSESSMENT

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

CLINICAL ASSESSMENT

1 INTRODUCTION

The clinical role of alendronate in the proposed indication, treatment of osteoporosis in post-menopausal women, is well established and the mechanism of action is as outlined in section II.2 Pharmacodynamics.

The original formulation was a 5 or 10mg tablet taken once daily. More recently a 70mg once weekly, tablet has been authorised, which has advantages in terms of convenience and limits the risk of upper GI side-effects because of the reduced frequency of administration.

The dossier summarises the clinical literature with regard to efficacy and safety of alendronate and the Applicant has submitted a single bioequivalence study.

1.1 GCP ASPECTS

The bioequivalence study supporting this application was conducted according to the Declaration of Helsinki (2000 and 2002 revisions) and the ICH note for guidance on Good Clinical Practice.

1.2 ORPHAN MEDICINAL PRODUCTS

N/A

2 CLINICAL PHARMACOLOGY

2.1 PHARMACOKINETICS

2.1.1 Introduction

In addition to active drug substance, monosodium alendronate trihydrate 91.36 mg (equivalent to 70mg of alendronate base) the proposed tablets contain the following excipients:

Cellactose 80
Croscarmellose sodium
Colloidal anhydrous silica and magnesium stearate

A single bioequivalence study has been conducted to support this application. It is described in Section II.1.2, below:

2.1.2 Absorption

Comparative dissolution profiles of the test 70mg alendronate tablet and 70mg Fosamax tablet in solutions of pH 1.0, 4.0 and distilled water show these match very closely for both products.

- **Bioequivalence**

A bioequivalence study comparing the test 70mg tablet with Fosamax® 70mg in healthy volunteers has been conducted:

Study 411-EC-03-10-0000

Title : Evaluation of the bioequivalence of two oral preparations containing 70mg alendronate (test product vs. Fosamax®70mg tablets, MSD Sharp &

Dohme GmbH, Germany). A monocentric, open, randomized, single dose, two-period crossover trial in healthy volunteers

Most alendronate is rapidly sequestered in bone following absorption and is only slowly released thereafter. Because of the difficulties of establishing the PK of alendronate after oral administration, much of the work in humans has been conducted with intravenous drug using urinary excretion data.

Because the oral bioavailability of alendronate is <1% and plasma levels are recognised to be too transient and too low for plasma measurement by even the most sensitive assays available, a bioequivalence study based on urinary recovery data was conducted, and this is an acceptable approach.

By calculating the maximum rate of excretion (R_{max}) a surrogate for C_{max} can be provided. However, from the work with alendronate, it is known that the majority of urinary excretion occurs within the first 12 h after administration, with very little excreted in the subsequent 12-36h period. The use of a 36h sampling period has therefore been used in this study.

After a 10h overnight fast, subjects were randomised to receive the Test or Reference products, taken with 240ml of tap water between 7-9 am on two separate occasions. A 14-20 day washout period was used.

Standard restrictions regarding food, fluids and exercise were applied and the first meal was 4 h after dosing.

Total urinary recovery was obtained by collecting urine over the following intervals after a 1.5 to 1h pre-dose collection:

0-15min, 15min-1h, 1-2h, 2-3, 3-4, 4-6, 6-8, 8-12, 12-24 and 24-36h post-dosing. The volume of urine collected in each interval was measured and two aliquots of equal volume were transferred into two 13ml transparent polypropylene tubes, immediately frozen and stored at a temperature <20°C until analysis.

Adverse events (AEs) during the study and clinical and laboratory screening were conducted.

HPLC with selective quantification of alendronate (LOQ 1ng/ml) was used to determine urinary concentrations of the drug. The analysts were blind as to the treatment each subject received on either occasion.

From these data, the primary target parameters of Ae_{0-36h} (amount of drug excreted in 0-36h urine post-dosing) and R_{max} (maximum rate of excretion) of alendronate were determined for the two formulations.

The evaluation of bioequivalence was based on a parametric method (ANOVA-log). An equivalence range of 80-125% for the 90% CIs for the primary parameters Ae_{0-36h} and R_{max} (log transformed data) was defined.

The 90% CI of log-transformed values was calculated for the intra-individual ratio test vs. Reference for Ae0-36h and R_{max} of alendronate and then compared with the corresponding C_{is} for Ae0-36h 80-125% and for R_{max} 80-125%.

The PK results are shown in Tables 1 and 2:

Table 1 : PK parameters

Test					
Variable	Geom. Mean	Arith.mean	SD	Range	Median
Ae0-36h [µg]	160.84	205.92	165.80	17.38 – 918.04	158.81
R _{max} [µg/h]	57.62	75.71	61.52	4.73 – 348.91	56.55
T _{max} [h]	-	0.97	0.60	0.13 – 3.50	0.63
Reference					
Variable	Geom. Mean	Arith.mean	SD	Range	Median
Ae0-36h [µg]	146.33	183.54	138.20	28.53-756.56	157.22
R _{max} [µg/h]	53.82	68.92	50.72	2.64 -278.63	57.42
T _{max} [h]	-	0.99	0.65	0.13 – 3.50	0.63

Table 2 bioequivalence analyses

Parameter	Point estimator Means Ratio Test : Ref	90% CIs	ANOVA – log CV%
Ae0-36h (µg)	1.10	0.97-1.24*	52.60
R _{max} (µg/h)	1.07	0.94-1.22*	54.24
T _{max} [h] (difference test- reference)	0.00	0.00 -0.00**	-

*ANOVA-log CI

** non-parametric CI

The 90% CI for Ae0-36h and R_{max} were both within the pre-specified standard bioequivalence parameters of 80-125% confirming bioequivalence.

Safety is discussed in section IV.

• Influence of food

It is well-known that food has a profound effect on absorption and the SPC addresses this and is consistent with that of Fosamax 70mg.

2.1.3 Distribution

Alendronate binds predominantly to serum albumin and the extent of bindings is influenced by pH and Ca⁺⁺ concentration. It is also species dependent – the unbound fraction of alendronate being around 22% in man. It becomes highly bound to bone, preferentially to sites with a high turnover rate.

2.1.4 Elimination

This is well characterised for alendronate and has been well reviewed by the Clinical Expert.

- **Excretion**

Renal clearance is around 71ml/min with a Vdss of at least 28L (exclusive of bone). Biliary excretion does not occur.

- **Metabolism**

Alendronate is not metabolised.

2.1.5 Pharmacokinetics in target population

The dosing recommendations are consistent with those of Fosamax 70mg.

- **Children**

N/A

Assessor's overall comments on pharmacokinetics in special populations

The SPC is consistent with that of Fosamax® 70mg i.e. No dosing adjustment is necessary in the elderly or those with renal impairment unless GFR < 35ml/min in which case alendronate is not recommended, due to lack of experience in this group.

2.1.6 Interactions

These have been well characterised for alendronate and the SPC is consistent with that of Fosamax® 70mg.

2.1.7 Assessor's overall conclusions on pharmacokinetics

The PK of alendronate has been well characterised and no new studies have been undertaken, apart from study 411-EC-03-10-000, which has confirmed the bioequivalence of the proposed product with Fosamax® 70mg.

2.2 PHARMACODYNAMICS

2.2.1 Introduction

ATC Code : M05B A04

Class : bisphosphonate, for the treatment of bone diseases.

2.2.2 Mechanism of action

This has been well characterised for alendronate: inhibition of osteoclastic bone resorption with no effect on bone formation, particularly at sites of active resorption. Qualitatively normal bone is formed.

2.2.3 Primary pharmacology

Alendronate is about 700 times more potent than etidronate, 100 times more potent than clodronate and 10 times more potent than pamidronate *in vivo* although the PK are similar to other bisphosphonates.

2.2.4 Assessor's overall conclusions on pharmacodynamics

The PD profile of alendronate has been well characterised and no new studies have been undertaken and none are required.

3 CLINICAL EFFICACY

3.1 ASSESSOR'S OVERALL CONCLUSIONS ON CLINICAL SAFETY

The efficacy of alendronate has been well reviewed by the Clinical Expert who is medically qualified. Given the demonstration of bioequivalence, the efficacy data on Fosamax[®] 70mg can be extrapolated to that of the proposed product. No new studies have, therefore, been conducted and none are required.

4 CLINICAL SAFETY

4.1 INTRODUCTION

The safety profile of alendronate has been well characterised and has been well reviewed by the Clinical Expert. Safety and tolerability has been evaluated in placebo-controlled clinical studies in over 17,000 women and men and also in a non-interventional pharmacovigilance study involving treatment in almost 12,000 patients. In addition, the drug has been prescribed in > 3 million patients. The bioequivalence study has provided additional data comparing the proposed product with Fosamax[®] 70mg.

4.2 EXPOSURE

The subjects in study were treated with trial medication and exposed to one single oral dose of 70mg alendronate (corresponding to one tablet of the test preparation or the reference drug) in each period of the trial. The total exposure for the volunteers was 140mg per volunteer.

4.3 ADVERSE EVENTS

During the bioequivalence study, a total of 40 AEs were reported in the volunteers. 17 were associated with the Test and 22 associated with the reference product. The remaining AE occurred pre-dosing so was not associated with treatment. For the test product, nausea was the most frequently reported AE with a time to onset of 30min to almost 5 h after dosing. They resolved spontaneously within three hours. Abdominal pain fatigue, headache, muscle cramp and vomiting were also reported. Gastrointestinal symptoms are a known side-effect of alendronate therapy.

For the reference product, nausea, abdominal pain and vomiting were reported.

4.4 SERIOUS ADVERSE EVENTS AND DEATHS

None were reported in the bioequivalence study carried out.

4.5 LABORATORY FINDINGS/VITAL SIGNS/ECG

From the bioequivalence study, there were a number of isolated minor out-of-range laboratory findings in a range of different parameters both before and after study treatment which were not considered by the Investigator to be of clinical relevance.

There were no reported treatment-related abnormalities in vital signs or ECG recordings.

4.6 POST MARKETING EXPERIENCE

At the time of filing, alendronate has been prescribed in > 3 million patients and no new safety concerns have arisen.

4.7 ASSESSOR'S OVERALL CONCLUSIONS ON CLINICAL SAFETY

From the bioequivalence study, the safety profile of the proposed product has been found to be similar to that of Fosamax[®] and is consistent with the known profile of the

drug. Given the demonstration of bioequivalence between the proposed product and Fosamax[®] 70mg, the safety profile of the latter may be extrapolated and the SPC sections are consistent between the two.

5 SPC

This is satisfactory and is consistent with the reference product.

6 PIL

This is satisfactory and is consistent with the reference product. The marketing authorisation holder has provided a commitment to update the marketing authorisation with a package leaflet in compliance with Article 59 of Council Directive 2001/83/EC and that the leaflet shall reflect the results of consultation with target patient groups, no later than 1st July 2008.

7 LABEL

This is satisfactory.

8 CONCLUSIONS AND BENEFIT/RISK ASSESSMENT

The proposed product, Alendronate 70mg Tablets, have been shown to be bioequivalent to the reference product Fosamax[®] 70mg Once Weekly tablets, therefore safety and efficacy can be extrapolated from the latter. The requirements of essential similarity have been met. The benefit-risk assessment is therefore favourable, and a Marketing Authorisation may be granted.

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 an application of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Alendronic Acid 70mg Tablets and Fosamax[®] 70mg tablets, MSD Sharp & Dohme GmbH, Germany. No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for Fosamax[®] 70mg tablets.

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's 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 16002/0075**

STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation applications on 30 th November 2004.
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 25 th November 2004.
3	Following assessment of the applications the MHRA requested further information relating to the quality dossiers on 25 th November 2004, 12 th December 2004 and 15 th August 2006.
4	The applicant responded to the MHRA's requests, providing further information on 7 th December 2004, 19 th December 2004 and 26 th November 2006 for the quality sections.
5	The applications were determined on 19 th March 2007.

**ALENDRONIC ACID 70MG TABLETS
PL 16002/0075**

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome
13/12/2007	Cancellation	Cancellation of licence to take effect from 12 th June 2008.	Approved on 13/12/2007

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 sodium trihydrate).

Each tablet contains 192.03 mg of lactose (as cellectose 80).'

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

White, round, biconvex conventional tablets, marked with '70' on one side and plain 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 use.

The recommended dosage is one 70 mg tablet once weekly.

To permit adequate absorption of alendronic acid:

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 alendronic acid (see section 4.5).

To facilitate delivery to the stomach and thus reduce the potential for local and oesophageal irritation/adverse experiences (see section 4.4):

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 section 4.4).

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

Use in renal impairment: No dosage adjustment is necessary for patients with a glomerular filtration rate (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: Alendronic acid 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.

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 alendronic acid or to any of the excipients.

Hypocalcaemia.

See also section 4.4.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Alendronic acid 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 alendronic acid 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 section 4.3).

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 alendronic acid. Physicians should therefore be alert to any signs or symptoms signalling a possible oesophageal reaction and patients should be instructed to discontinue alendronic acid 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 alendronic acid properly and/or who continue to take alendronic acid 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 section 4.2). 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.

Alendronic acid is not recommended for patients with renal impairment where GFR is less than 35 ml/min, (see section 4.2).

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

Hypocalcaemia must be corrected before initiating therapy with alendronic acid (see section 4.3). 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 Alendronic Acid 70 mg Tablets.

Due to positive effects of alendronic acid 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.

With reference to the presence of lactose monohydrate in the formulation, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 bisphosphonates therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of 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 alendronic acid. Therefore, patients must wait at least 30 minutes after taking alendronic acid before taking any other oral medicinal product (see sections 4.2 and 5.2).

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 alendronic acid. No adverse experiences attributable to their concomitant use were identified.

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

4.6 PREGNANCY AND LACTATION

Pregnancy

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

Lactation

It is not known whether alendronic acid is excreted into human breast milk. Given the indication, alendronic acid 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 Alendronic Acid 70 mg tablets (n=519) and alendronic acid 10 mg/day (n=370) were similar.

In two three-year studies of virtually identical design, in post-menopausal women (alendronic acid 10 mg: n=196, placebo: n=397) the overall safety profiles of alendronic acid 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 alendronic acid 10 mg/day and at a greater incidence than in patients given placebo in the three-year studies:

	One-Year Study		Three-Year Studies	
	Alendronic Acid 70 mg once weekly (n = 519) %	Alendronic Acid 10 mg/day (n = 370) %	Alendronic Acid 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 with the following frequencies:

Very common ($\geq 10\%$),
 common ($\geq 1\%$ and $< 10\%$),
 uncommon ($\geq 0.1\%$ and $< 1\%$),
 rare ($\geq 0.01\%$ and $< 0.1\%$),
 very rare ($< 0.01\%$) including isolated reports

Blood and the lymphatic system disorders:

Rare: symptomatic hypocalcaemia, often in association with predisposing conditions (see section 4.4).

Immune system disorders:

Rare: 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.

Nervous system disorders:

Common: headache.

Eye disorders:

Rare: uveitis, scleritis, episcleritis.

Gastro-intestinal disorders:

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

Uncommon: nausea, vomiting, gastritis, oesophagitis*, oesophageal erosions*, melaena.

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

Skin and subcutaneous tissue disorders

Uncommon: rash, pruritus, erythema

Rare: Rash with photosensitivity.

Very rare: isolated cases of severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported.

Musculoskeletal, connective tissue and bone disorders:

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

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)

* See sections 4.4 and 4.2.

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 alendronic acid 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 alendronic acid. Milk or antacids should be given to bind alendronic acid. 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 Alendronic Acid 70 mg Tablets, alendronic acid sodium trihydrate, is a bisphosphonate that inhibits osteoclastic bone resorption with no direct effect on bone formation. Preclinical studies have shown preferential localisation of alendronic acid 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 alendronic acid 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 Alendronic Acid 70 mg Tablets (n=519) and alendronic acid 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 alendronic acid on bone mass and fracture incidence in post-menopausal women were examined in two initial efficacy studies of identical design (n=994) as well as in the Fracture Intervention Trial (FIT: n=6,459).

In the initial efficacy studies, the mean bone mineral density (BMD) increases with alendronic acid 10 mg/day relative to placebo at three years were 8.8%, 5.9% and 7.8% at the spine, femoral neck and trochanter, respectively. Total body BMD also increased significantly. There was a 48% reduction (alendronic acid 3.2% vs placebo 6.2%) in the proportion of patients treated with alendronic acid experiencing one or more vertebral fractures relative to those treated with placebo. In the two-year extension of these studies BMD at the spine and trochanter continued to increase and BMD at the femoral neck and total body were maintained.

FIT consisted of two placebo-controlled studies using alendronic acid 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 alendronic acid daily reduced the incidence of ≥ 1 new vertebral fracture by 47% (alendronic acid 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 (alendronic acid 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 alendronic acid 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 alendronic acid was administered one hour or half an hour before a standardised breakfast. In osteoporosis studies, alendronic acid was effective when administered at least 30 minutes before the first food or beverage of the day.

Bioavailability was negligible whether alendronic acid was administered with, or up to two hours after, a standardised breakfast. Concomitant administration of alendronic acid 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 alendronic acid (a mean increase ranging from 20% to 44%).

Distribution

Studies in rats show that alendronic acid 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 alendronic acid is metabolised in animals or humans.

Elimination

Following a single intravenous dose of [14 C]alendronic acid, 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 alendronic acid 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 alendronic acid from the skeleton. Alendronic acid 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 alendronic acid via the kidney will be reduced in patients with impaired renal function. Therefore, somewhat greater accumulation of alendronic acid in bone might be expected in patients with impaired renal function (see section 4.2).

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 alendronic acid 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

Cellactose 80
Croscarmellose sodium
Colloidal anhydrous silica
Magnesium stearate

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

2 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

No special precautions for storage.

6.5 NATURE AND CONTENTS OF CONTAINER

PVC/aluminum blisters in packs containing 2, 4 or 12 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Pharmafile Ltd
Medici House
Ashbourne Industrial Estate
Ashbourne,
Co. Meath
Ireland

8 MARKETING AUTHORISATION NUMBER(S)

PL 16002/0075

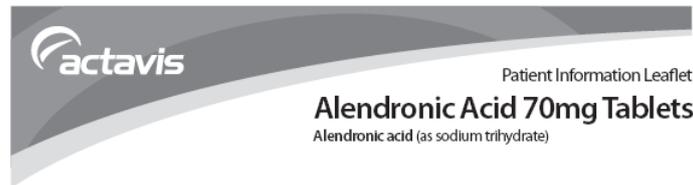
9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/03/2007

10 DATE OF REVISION OF THE TEXT

19/03/2007

PATIENT INFORMATION LEAFLET



- Please read this leaflet carefully before you start to take your tablets.
- It contains important information.
- It is particularly important to read the section "How to take your tablets".
- If you are not sure about anything, or want to know more, ask your doctor or a pharmacist.
- Keep this leaflet safe, as you may want to read it again.

ABOUT YOUR TABLETS

Your tablets are called Alendronic Acid 70mg Tablets. They are part of a group of drugs known as bisphosphonates.

WHAT IS IN YOUR TABLETS

Each tablet contains:

- Alendronic acid 70mg (as sodium trihydrate) (active ingredient); and
- Cellactose 80, croscarmellose sodium, colloidal anhydrous silica and magnesium stearate (inactive ingredients).

Alendronic Acid 70mg Tablets are white, round, biconvex tablets, marked with '70' on one side and plain on the other side. Alendronic Acid 70mg Tablets are supplied in blister packs of 2, 4 and 12 tablets. Not all pack sizes may be marketed.

Who makes your tablets

The marketing authorisation holder is Pharmfile Ltd, Medici House, Ashbourne Industrial Estate, Ashbourne, Co.Meath, Ireland. The manufacturer and distributor is Actavis Barnstaple, EX32 8NS, UK.

What your tablets do

Alendronic acid belongs to a group of medicines called bisphosphonates. Alendronic acid prevents the loss of bone (osteoporosis) in women that occurs after the menopause, and helps to rebuild bone. Osteoporosis if untreated can result in fractures (broken bones) of the spine and hips, and alendronic acid can reduce the risk of the fractures occurring.

BEFORE YOU TAKE YOUR TABLETS

Do not take Alendronic Acid 70mg Tablets and tell your doctor if;

- you have certain disorders of the oesophagus (sometimes called the gullet and is the tube that connects your mouth with your stomach)
- you are unable to stand or sit upright for at least 30 minutes
- you are allergic to any of the ingredients

- your doctor has told you that you have low blood calcium
 - you are or think you may be pregnant
 - you are breast-feeding.
- Alendronic acid should not be given to children.

Please tell your doctor or pharmacist before you start to take Alendronic Acid 70mg Tablets if you;

- suffer from kidney problems
- have any allergies
- have any swallowing or digestive problems
- have an intolerance to some sugars e.g. lactose
- are taking any other medicines including ones you have bought yourself without prescription.

Can you take Alendronic acid with other medicines?

Alendronic acid can interact with food, drinks and other medicines which you take by mouth, and it is important to follow the advice given under the heading "How to take your tablets". You should always tell your doctor about all medicines you are taking or plan to take, including any obtained without prescription.

HOW TO TAKE YOUR TABLETS

Alendronic Acid 70mg Tablets are to be taken by mouth once a week. It is important that you carefully follow the instructions on how to take your tablets.

Choose a day of the week to take your tablet that best fits with your normal schedule. Every week, take one Alendronic Acid 70mg Tablet on your chosen day. After getting up for the day and before taking your first food, beverage or other medicine, swallow your Alendronic Acid 70mg Tablet with a full glass of plain water (not less than 200ml or 7 fl. oz).

Do not take your tablet with mineral water, coffee, tea or fruit juice.

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

After swallowing your 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.

Do not take Alendronic acid at bedtime or before getting up for the day. If you develop difficulty or pain upon swallowing, chest pain, or new or worsening heartburn, stop taking Alendronic acid and contact your doctor. After swallowing your Alendronic Acid 70mg Tablet, wait at least 30 minutes

ECZPL000

before taking your first food, beverage, or other medication of the day, including antacids, calcium supplements and vitamins. Alendronic acid is effective only if taken when your stomach is empty. If you miss a dose, just take one Alendronic Acid 70mg Tablet on the morning after you remember. **Do not take two tablets on the same day.** The following week return to taking one tablet once a week, as originally scheduled on your chosen day. It is important that you continue taking Alendronic acid for as long as your doctor prescribes the medicine.

What to do if you take too many tablets

It is important not to take too many tablets. If you have taken too many tablets drink a full glass of milk and contact your doctor or hospital Accident and Emergency department immediately. Do not make yourself vomit, and do not lie down.

What unwanted effects could Alendronic Acid 70mg Tablets have?

While taking Alendronic Acid 70mg Tablets you may have some side effects. Tell your doctor if you suffer from any of the following:

- irritation or ulceration of the oesophagus (the 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. These reactions may occur if patients do not drink a full glass of water with alendronic acid and/or if they lie down less than 30 minutes after taking alendronic acid or before their first food of the day. Oesophageal reactions may worsen if patients continue to take alendronic acid after developing symptoms suggesting irritation of the oesophagus.
- stomach/abdominal pain, dyspepsia, constipation, diarrhoea, flatulence, feeling full or bloated, nausea and vomiting and black and/or bloody stools.
- some patients may experience bone, muscle or joint pain, (rarely, with flu-like symptoms or fever), headache or rarely a rash (occasionally made worse by sunlight), itching, eye pain, diminished or hazy vision and/or see black floating spots.
- rarely stomach or other peptic ulcers have occurred. It is not known whether or not these were caused by treatment with Alendronic acid.
- very rarely severe skin reactions have occurred. Allergic reactions such as hives or, rarely, more severe allergic reactions have occurred. If you experience swelling of the face, lips, tongue and/or throat, possibly causing difficulty in breathing or swallowing, you should go to your local Accident

and Emergency department immediately as this may be due to a severe allergic reaction which can be life threatening.

- mouth ulcers have occurred when the tablets have been chewed or sucked. If you feel unwell in any other way, tell your doctor as soon as you can. Alendronic acid should not affect your ability to drive or operate machinery.

LOOKING AFTER YOUR TABLETS

Keep all tablets out of the sight and reach of children.

No special storage conditions are required for this medicine.

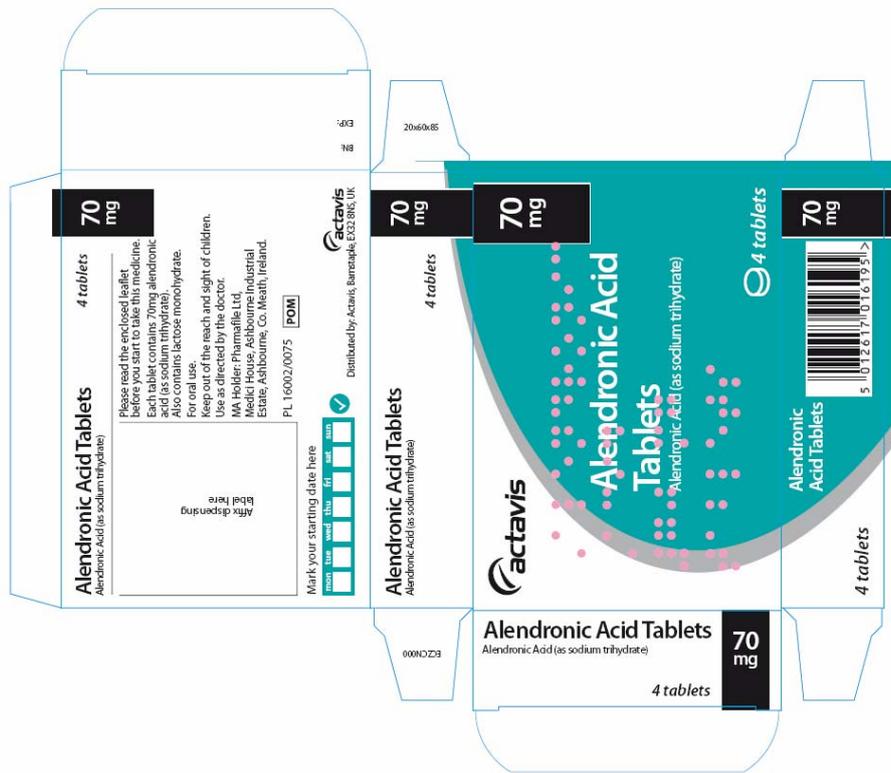
Do not take the tablets after the expiry date. You should take any tablets that are out of date or which you no longer need back to your pharmacist.

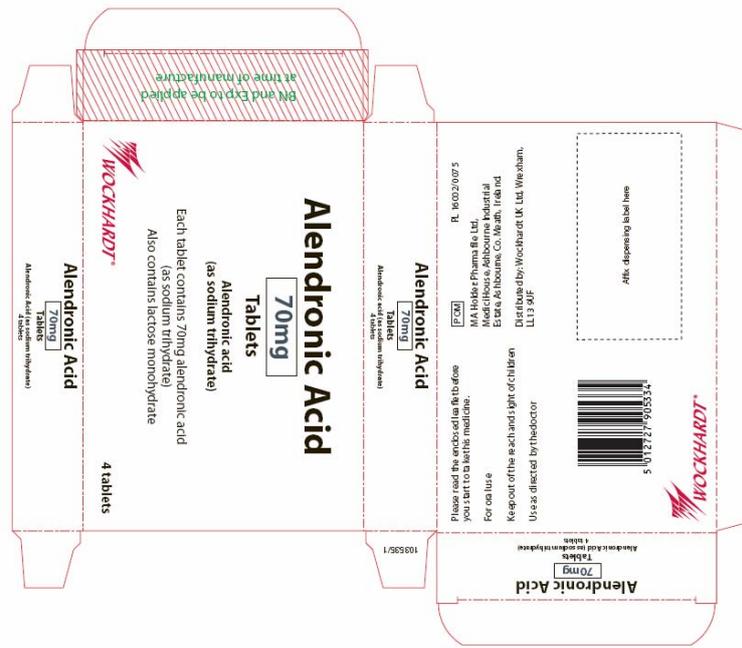
These tablets are only for you. Only a doctor can prescribe them for you. Never give them to anyone else as it may harm them, even if their symptoms are the same as yours.

PL number 16002/0075

This leaflet was written in August 2005.

LABELLING





<p>Alendronic Acid 70mg Tablets Alendronic acid (as sodium trihydrate) MA Holder: Pharmafie Ltd.</p>	<p>Alendronic Acid 70mg Tablets Alendronic acid (as sodium trihydrate) MA Holder: Pharmafie Ltd.</p>	<p>Alendronic Acid 70mg Tablets Alendronic acid (as sodium trihydrate) MA Holder: Pharmafie Ltd.</p>	<p>Alendronic Acid 70mg Tablets Alendronic acid (as sodium trihydrate) MA Holder: Pharmafie Ltd.</p>
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