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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency granted PLGenerics Limited a Marketing Authorisation (licence) for the medicinal product Alendronic Acid 70mg Tablets (PL 27784/0001) on the 13th December 2010. This is a prescription-only medicine (POM) for the treatment of postmenopausal osteoporosis.

Alendronic Acid 70mg 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 70mg Tablets outweigh the risks; hence a Marketing Authorisation has been granted.
ALENDRONIC ACID 70 MG TABLETS
PL 27784/0001

SCIENTIFIC DISCUSSION

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Introduction Page 4
Pharmaceutical assessment Page 5
Preclinical assessment Page 8
Clinical assessment (including statistical assessment) Page 9
Overall conclusions and risk benefit assessment Page 11
INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted a marketing authorisation for the medicinal product Alendronic Acid 70mg Tablets (PL 27784/0001) on 13th December 2010. This is a prescription-only medicine (POM).

This is a national application for Alendronic Acid 70mg Tablets submitted under Article 10.1 of Directive 2001/83/EC, as amended, which have been shown to be a generic medicinal product of Fosamax Once Weekly 70mg Tablets (PL 00025/0399), authorised to Merck, Sharpe and Dohme Ltd., 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.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Sodium alendronate

INN: Sodium Alendronate

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

Structure:

\[
\begin{align*}
\text{Structure:} & \\
\text{Molecular formula:} & C_4H_{12}N\text{Na}O_7P_2.3\text{H}_2\text{O} \\
\text{Relative molecular mass:} & 325.1 \\
\text{Description:} & \text{A white or almost white crystalline powder, soluble in water, very slightly soluble in methanol, practically insoluble in methylene chloride.} \\
\end{align*}
\]

Sodium Alendronate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance sodium alendronate trihydrate are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

DRUG PRODUCT

Description and Composition

Alendronic Acid 70mg Tablets are presented as white oblong, biconvex tablets. Each tablet contains 70mg alendronic acid (as sodium alendronate trihydrate).

Other ingredients consist of pharmaceutical excipients, namely lactose monohydrate, cellulose microcrystalline, croscarmellose sodium, silica, colloidal anhydrous and magnesium stearate. All excipients used comply with their respective Ph Eur monograph. Satisfactory certificates of analysis have been provided for all excipients. Appropriate justification for the inclusion of each excipient has been provided. The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as those intended for human consumption.
Pharmaceutical development
Details of the pharmaceutical development of the medicinal product have been supplied and are satisfactory. The objective was to develop a stable, generic formulation, with similar physical and chemical characteristics to the reference product, Fosamax Once Weekly 70mg Tablets.

Dissolution and Impurity profiles
Comparative dissolution and impurity data were provided for the test and reference products. The dissolution and impurity profiles were found to be similar and were satisfactory.

Manufacture
A detailed 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 pilot-scale batches of product 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
The finished product is licensed for marketing in aluminium/polyvinylchloride (Al/PVC) blister packs, which are placed with the Patient Information Leaflet (PIL) into cardboard outer cartons in pack sizes of 2, 4, 8, 12 or 40 tablets. The MAH has stated that not all pack sizes may be marketed and has committed to submit mock-ups for all packaging for assessment before those pack sizes are commercially marketed. All primary packaging complies with Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years has been set, with no specific storage conditions, which is acceptable.

Bioequivalence Study
A bioequivalence study was presented comparing the test product, Alendronic Acid 70mg Tablets, to the reference product, Fosamax Once Weekly 70mg Tablets (Merck, Sharp & Dohme Ltd).

An evaluation of the bioequivalence study is found in the Clinical Section of this report.

Quality Overall Summary
A satisfactory quality overview is provided and has been prepared by an appropriately qualified expert. The curriculum vitae of the expert has been provided.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels

The SmPC, PIL and labelling are pharmaceutically acceptable. Colour mock-ups of the labelling and PIL have been provided. The labelling is satisfactory and fulfils the statutory requirements for Braille.

The applicant has submitted results of PIL user-testing. 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 upon the information that the leaflet contains.

MAA Form
The MAA form is pharmaceutically satisfactory.

Conclusion
The test product corresponds to the current EU definition of a generic medicinal product because it complies with the criteria of having the same qualitative and quantitative composition in terms of the active substance and pharmaceutical form. On this basis and considering the bioequivalence data provided, the applicant’s claim that Alendronic Acid 70mg Tablets is a generic medicinal product of Fosamax Once Weekly 70mg (Merck, Sharp & Dohme Ltd-PL 00025/0399), is justified.

There are no objections to approval of Alendronic Acid 70mg Tablets from a pharmaceutical point of view.
PRECLINICAL ASSESSMENT

No new non-clinical studies were performed, which is acceptable given that the proposed product is a generic medicinal product an originator product that has been licensed for over 10 years.

NON-CLINICAL EXPERT REPORT
The non-clinical expert report has been written by an appropriately qualified person is satisfactory, providing an appropriate review of the non-clinical aspects of the dossier.

ENVIRONMENTAL RISK ASSESSMENT
An environmental risk assessment was not submitted and none is required for this application. This is acceptable given that this product is intended for generic substitution with the market leaders and, as such, will be used instead of not additional to other such products on the market (thus not increasing any environmental impact).

CONCLUSION
The grant of a Marketing Authorisation is recommended.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
The clinical pharmacology of alendronate is well-known. With the exception of the bioequivalence study, no new pharmacodynamic or pharmacokinetic data are supplied and none are required for this application.

PHARMACOKINETICS
In support of this application, the marketing authorisation holder has submitted the following bioequivalence study:

Study:
A randomized, 2-way, crossover, bioequivalence study of Alendronic Acid 70 mg tablets and Fosamax Once Weekly, 70mg Tablets (Merck, Sharpe & Dohme Ltd., UK-PL 00025/0399) administered as 1 x 70 mg tablet in healthy subjects under fasting conditions. The study was conducted in compliance with Good Clinical Practice.

Subjects were dosed with either treatment after at least a 10-hour fast. Urine samples were taken pre- and up to 36 hours post dose in each treatment period. The wash-out period between the two treatments was 21 days. Pharmacokinetics parameters were measured from plasma and statistically analysed. The statistical analysis consisted of Ln-transformed $A_{e0-36}$ and $R_{max}$ and Parametric ANOVA on $A_{e0-36}$ and $R_{max}$.

Results:
The pharmacokinetic results for alendronic acid are presented below:

<table>
<thead>
<tr>
<th></th>
<th>Test A (Alendronate)</th>
<th>Reference B (Fosamax)</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A_{e0-36}$ (µg)</td>
<td>202.24± 140.01</td>
<td>219.12± 238.87</td>
<td>86.73-109.77</td>
</tr>
<tr>
<td>$R_{max}$ (µg/h)</td>
<td>65.28± 46.05</td>
<td>69.11± 57.60</td>
<td>83.71-105.74</td>
</tr>
<tr>
<td>$T_{max}$ (h)</td>
<td>1.06± 0.54</td>
<td>0.925± 0.479</td>
<td>-</td>
</tr>
</tbody>
</table>

The applicant has chosen to use urinary excretion data. The bioequivalence guidelines from CPMP state that 'the use of urine excretion data may be advantageous in determining the extent of drug input in cases of products predominantly excreted renally, but has to be justified when used to estimate the rate of absorption'. In 2003, when this study was carried out, the use of urinary data was the standard protocol for bisphosphonate bioequivalence studies.

Conclusion of Bioequivalence:
The results of the bioequivalence study show that the test product, Alendronic Acid 70 mg Tablets, and the reference product, Fosamax Once Weekly 70mg tablets are bioequivalent, under fasting conditions as the confidence intervals for $A_{e0-36}$ and $R_{max}$ are within 80-125% limits. This is satisfactory. The appearance of the individual urinary concentration curves was similar for the urinary excretion rate profile of alendronic acid for both products.

Clinical efficacy
No new data have been submitted and none are required. The reference product is established and the application depends upon the ability to demonstrated
bioequivalence. Efficacy is reviewed in the clinical overview. The efficacy of alendronic acid is well-established from its extensive use in clinical practice.

**Clinical safety**
No new data have been submitted and none are required for applications of this type. No new or unexpected safety concerns arose from this application. Safety is reviewed in the clinical overview. The safety profile of alendronate is well-known.

**PRODUCT INFORMATION:**
**Summary of Product Characteristics (SmPC)**
The approved SmPC is consistent with that of the innovator product and is acceptable.

**Patient Information Leaflet (PIL)**
The final PIL is in-line with the approved SmPC and is satisfactory.

**Labelling**
The labelling is satisfactory.

**Clinical Overview**
A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. The CV of the clinical expert has been supplied.

**RISK MANAGEMENT PLAN**
A suitable justification has been provided for not submitting a risk management plan for this product.

**CONCLUSIONS:**
Sufficient clinical information has been submitted to support this application. The benefit-risk of the product is considered favourable from a clinical perspective. The grant of a Marketing Authorisation was therefore recommended on medical grounds.
OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Alendronic Acid 70mg Tablets is 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 the reference product, Fosamax Once Weekly 70mg tablets.

SAFETY
No new or unexpected safety concerns arise from this application.

The SmPC, PIL and labelling are satisfactory and consistent with that for the innovator product.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with sodium alendronate is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
**ALEDRONIC ACID 70 MG TABLETS**
**PL 27784/0001**

**STEPS TAKEN FOR ASSESSMENT**

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation application on 12(^{th}) May 2006.</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 15(^{th}) September 2006.</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the applications the MHRA requested further information relating to the clinical dossiers on 10(^{th}) November 2006, and further information relating to the quality dossiers on 27(^{th}) March 2007 and 16(^{th}) July 2010.</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 6(^{th}) January 2007 for the clinical sections, and again on 3(^{rd}) March 2009 and 22(^{nd}) October 2010 for the quality sections.</td>
</tr>
<tr>
<td>5</td>
<td>The application was determined on 13(^{th}) December 2010.</td>
</tr>
</tbody>
</table>
### STEPS TAKEN AFTER AUTHORISATION - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
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<tbody>
<tr>
<td></td>
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<tr>
<td></td>
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</tr>
</tbody>
</table>
1 NAME OF THE MEDICINAL PRODUCT
Alendronic acid 70 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains Alendronic acid 70 mg (as sodium alendronate trihydrate).
Each tablet contains lactose monohydrate.
For full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM
Tablet.
White, oblong, biconvex tablets.

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Treatment of postmenopausal osteoporosis. Alendronate 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.

Adults only:

To permit adequate absorption of alendronate:

Alendronate 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'):

- Alendronate 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 Alendronate tablets.

Alendronate 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').

Elderly (more than 65 years):

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.
Renal Impairment:

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

Children (under 18 years):

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

Alendronate 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'). In patients with known Barrett's oesophagus, prescribers should consider the benefits and potential risks of alendronate on an individual patient basis.

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 Alendronate 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 'Contraindications'). 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 tablets.

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 this patients with cancer receiving treatment regiments including primarily intravenously administered bisphosphonates. Many of these patients were also receiving chemotherapy and 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 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.

Contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 hypocalcaemia (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

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
Alendronate 70 mg tablets (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 ≥1% in either treatment group in the one-year
study, or in ≥1% of patients treated with alendronate 10 mg/day and at a greater incidence
than in patients given placebo in the three-year studies:

<table>
<thead>
<tr>
<th>One-year study</th>
<th>Three-year studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alendronate 70 mg weekly (n=519)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>%</td>
</tr>
<tr>
<td>Stomach pain</td>
<td>3.7</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>2.7</td>
</tr>
<tr>
<td>Acid reflux</td>
<td>1.9</td>
</tr>
<tr>
<td>Nausea</td>
<td>1.9</td>
</tr>
<tr>
<td>Bloated stomach</td>
<td>1.0</td>
</tr>
<tr>
<td>Constipation</td>
<td>0.8</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0.6</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>0.4</td>
</tr>
<tr>
<td>Flatulence</td>
<td>0.4</td>
</tr>
<tr>
<td>Gastritis</td>
<td>0.2</td>
</tr>
<tr>
<td>Ulcers</td>
<td>0.0</td>
</tr>
<tr>
<td>Esophageal ulcers</td>
<td>0.0</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>%</td>
</tr>
<tr>
<td>Musculoskeletal pain (bone, muscle or joint)</td>
<td>2.9</td>
</tr>
<tr>
<td>Muscle cramps</td>
<td>0.2</td>
</tr>
<tr>
<td>Neurological</td>
<td>%</td>
</tr>
<tr>
<td>Headache</td>
<td>0.4</td>
</tr>
</tbody>
</table>
The following adverse experiences have also been reported during clinical studies and/or post-marketing use:

**Common (≥1/100, <1/10)**

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

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

*Neurological*: headache.

**Uncommon (≥1/1,000, <1/100)**

*Body as a whole*: rash, pruritus, erythema.

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

**Rare (≥1/10,000, <1/1,000)**

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

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

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 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.

*Special senses*: uveitis, scleritis, episcleritis.

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

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

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

**Laboratory test findings**

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

### 4.9 OVERDOSE

Hypocalcaemia, hypophosphataemia and upper gastro-intestinal adverse events, such as upset stomach, heartburn, oesophagitis, gastritis, or ulcer, may result from oral overdosage.
No specific information is available on the treatment of overdosage with alendronate. Milk or antacids should be given to bind alendronate. Owing to the risk of oesophageal irritation, vomiting should not be induced and the patient should remain fully upright.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Bisphosphonate, for the treatment of bone diseases; ATC code: M05B A04

The active ingredient of Alendronate 70 mg tablets, 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 70 mg tablets (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
Lactose monohydrate
Cellulose microcrystalline
Croskarmellose sodium
Silica, colloidal anhydrous
Magnesium stearate

6.2 INCOMPATIBILITIES
Not applicable

6.3 SHELF LIFE
3 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE
No special storage conditions.

6.5 NATURE AND CONTENTS OF CONTAINER
Al/PVC blister packs.
Pack sizes may include 2, 4, 8, 12 or 40 tablets. Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
No special requirements.

7 MARKETING AUTHORISATION HOLDER
PLGENERICS LIMITED
Dorset House Regent Park, 297 Kingston Road
Leatherhead, Surrey KT22 7PL, United Kingdom

8 MARKETING AUTHORIZATION NUMBER(S)
PL 27784/0001

9 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
13/12/2010

10 DATE OF REVISION OF THE TEXT
13/12/2010
ALEDNRONIC ACID 70 MG TABLETS
PL 27784/0001

PACKAGE LEAFLET: INFORMATION FOR THE USER

Alendronic acid 70 mg Tablets
(Sodium alendronate 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 any further questions, 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.

In this leaflet:
1. What Alendronic acid 70 mg Tablets is and what it is 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 ALEDNRONIC ACID 70 MG TABLETS IS AND WHAT IT IS USED FOR

Alendronic acid 70 mg Tablets helps to rebuild bone and prevent the loss of bone that occurs in women after they have been through menopause. Alendronic acid 70 mg Tablets reduces the risk of spine and hip fractures.

Your doctor has prescribed Alendronic acid 70 mg Tablets because you have a disease called osteoporosis.

What is osteoporosis?

Osteoporosis is a thinning and weakening of the bones. It is common in women after menopause. At menopause, ovaries stop producing the female hormone, oestrogen, which helps to keep a woman’s skeleton healthy. As a result, bone loss occurs and bones become weaker. The earlier a woman reaches menopause, the greater the risk of osteoporosis.

In the early stages osteoporosis usually has no symptoms. If left untreated, however, it can result in fractures (broken bones). Although most often fractures cause pain, fractures of the bones in the spine may not be noticed until there is significant height loss.

With osteoporosis, fractures may occur during normal, everyday activity, such as lifting, or from minor injury that is not sufficient to fracture normal bone. Fractures usually occur at the hip, spine, or wrist and can lead not only to pain but also to considerable deformity and disability (such as stooped posture, or ‘dowager’s hump’, and loss of mobility).

Alendronic acid 70 mg Tablets belong to a group of non-hormonal medicines called bisphosphonates.
How can osteoporosis be treated?

Osteoporosis can be treated and it is never too late to begin. Your doctor has prescribed Alendronic acid 70 mg Tablets to treat your osteoporosis.

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

These are:

- **Stop smoking** – Smoking appears to increase the rate at which you lose bone and may increase your risk of fracture.
- **Exercise** – Like muscles, 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

Always tell your doctor about all medications you are taking, or plan to take, including those obtained without a prescription.

**Alendronic acid 70 mg Tablets should not be given to children.**

Do not take Alendronic acid 70 mg Tablets if:

- you have certain disorders of the oesophagus (the tube that connects your mouth to your stomach)
- you are unable to stand or sit upright for at least 30 minutes
- you are allergic to any of the ingredients
- if you are lactose intolerant
- your doctor has told you that you have low blood calcium
- you are, or think you may be, pregnant
- you are breastfeeding.

If you think any of these apply to you, do not take the tablets. Talk to your doctor first and follow the advice given.

You must tell your doctor before taking Alendronic acid 70 mg Tablets if:

- you suffer from kidney problems
- you have any allergies
- you have swallowing or digestive problems
- if your doctor has told you that you have Barrett’s oesophagus (a condition associated with changes in the cells that line the lower oesophagus)
- you are suffering from cancer and/or are undergoing any treatment for cancer, such as chemotherapy, radiotherapy, etc. You may need to visit your dentist before starting on Alendronate
- you need to see your dentist for any reason.
- you are taking corticosteroids for any reason.

Taking Alendronic acid 70 mg Tablets with food and drink

Alendronic acid 70 mg Tablets can interact with food, drinks and other medications which you take by mouth. It is important that you follow the advice given under the heading ‘How to take Alendronic acid 70 mg Tablets’.

Pregnancy and breastfeeding

Always 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.

Lactose intolerance

This medicine contains lactose. If you are lactose intolerant or sensitive, contact your doctor before taking this medicinal product.

3. HOW TO TAKE ALENDRONIC ACID 70 MG TABLETS

Always take Alendronic acid 70 mg Tablets exactly as your doctor has instructed you. If you are unsure about how to take Alendronic acid 70 mg Tablets, check with your doctor or pharmacist. You may previously have been prescribed a 10 mg tablet of alendronate which is taken once a day. The usual dose of Alendronic acid 70 mg Tablets is one tablet taken once a week.

Do the following to help ensure you will benefit from Alendronic acid 70 mg Tablets.
If you do not follow these steps and directions, you are more likely to suffer from side effects (see Section 4. Possible Side Effects).

1. **Choose a day.** Choose the day of the week that best fits your schedule. On the same chosen day once a week, take one Alendronate tablet 70 mg.

   It is very important that you follow steps 2, 3, 4 and 5 to help the Alendronate tablet 70 mg reach your stomach quickly and reduce potential for irritation of your oesophagus.

2. **Do not eat or drink.** After getting up for the day and before taking your first food, beverage, or other medication, swallow your Alendronate 70 mg tablet with a full glass of plain water only (not less than 200 ml or 7 fl. oz.). Do not use:
   - mineral water
   - coffee or tea
   - juice.
   - Do not chew or allow the tablet to dissolve in your mouth.

3. **Do not lie down.** Take Alendronate 70 mg tablet at the beginning of your day. Stay fully upright (sitting, standing or walking) for at least 30 minutes and do not lie down again until after your first food of the day. Do not take at bedtime or before getting up for the day.

4. **Do not eat.** After swallowing your Alendronate 70 mg tablet, wait at least 30 minutes before your first food, beverage, or other medication of the day, including antacids, calcium supplements and vitamins. Alendronate 70 mg tablet is effective only if taken when your stomach is empty.

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

6. **Continue your medication.** It is important that you take Alendronate acid 70 mg Tablets for as long as your doctor prescribes it. Alendronate 70 mg tablet can treat your osteoporosis only if you continue to take it.

   **If you take more Alendronic acid 70 mg Tablets than you should** 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,** just take one Alendronate tablet 70 mg on 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.
4. POSSIBLE SIDE EFFECTS

Most patients do not have side effects from taking Alendronic acid 70 mg Tablets. However, as with any medicine, Alendronic acid 70 mg Tablets may have unintended or undesirable effects.

If any of the following side effects become serious, contact your doctor.

Oesophageal and Gastrointestinal

Side effects usually have been mild, but some patients may experience severe digestive disturbances. These include irritation or ulceration of the oesophagus which can cause chest pain, heartburn, and/or scarring leading to narrowing of the oesophagus.

Tell your doctor immediately if you experience irritation of the oesophagus.

These reactions may occur especially if patients:
- do not drink a full glass of water with Alendronic acid 70 mg Tablets
- lie down less than 30 minutes after taking Alendronic acid 70 mg Tablets
- eat before taking Alendronic acid 70 mg Tablets or within 30 minutes of taking Alendronic acid 70 mg Tablets.

Oesophageal reactions may worsen if patients continue to take Alendronic acid 70 mg Tablets after developing symptoms suggesting irritation of the oesophagus.

Gastro-intestinal side-effects include: abdominal pain, dyspepsia (discomfort after eating), constipation, diarrhoea, difficulty in swallowing, flatulence, full or bloated feeling in the stomach, nausea and vomiting and black and/or bloody stools.

Some patients may experience jaw problems, often following tooth extraction.

Rarely stomach or other peptic ulcers have occurred, although some were severe and some bled. It is not known whether or not these were caused by treatment with Alendronic acid 70 mg Tablets or if there were other factors.

Ache / Pain

Some patients may experience bone, muscle or joint pain, headache, eye pain, diminished or hazy vision and/or see black floating spots, or inflammation of the eye. Flu-like symptoms or fever occur in rare cases.

Skin / Allergic

Isolated cases of severe skin reactions have occurred. A rash or itching may occur in rare cases (occasionally made worse by sunlight).

Allergic reactions, such as hives or rarely, swelling of the face, lips, tongue and/or throat possibly causing difficulty in breathing or swallowing, may occur.

Mouth ulcers (sores) have occurred as a result of the tablets being chewed or sucked.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist. It will help if you note what you experienced, when it started and how long it lasted.

5. HOW TO STORE ALENDRONIC ACID 70 MG TABLETS

- Keep your tablets out of the reach and sight of children.
- Do not use after the expiry date stated on the blister and carton.
- There are no special storage instructions.

6. FURTHER INFORMATION

What Alendronic acid 70 mg Tablets contains

The active substance in Alendronic acid 70 mg Tablets is alendronate (as sodium alendronate trihydrate). Each tablet contains the equivalent of 70 mg alendronate acid as 91.37 mg of alendronate sodium trihydrate.

The other ingredients are lactose monohydrate, cellulose microcrystalline, croscarmellose sodium, silica colloidal anhydrous, magnesium stearate.

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

Alendronic acid 70 mg Tablets are white, oblong, biconvex tablets.

Alendronic acid 70 mg Tablets are available in blister packs of 2, 4, 8, 12 or 40 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder
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Manufacturer
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This leaflet was last approved in
ALENDRONIC ACID 70 MG TABLETS
PL 27784/0001

LABEL

Blister foil

Outer carton