# ALENDRONIC ACID 70MG TABLETS

## PL 29831/0350

## UKPAR

## TABLE OF CONTENTS

# ALENDRONIC ACID 70MG TABLETS

# PL 29831/0350

## LAY SUMMARY

The MHRA granted Wockhardt UK Limited a Marketing Authorisation (licence) for the medicinal product Alendronic Acid 70 mg Tablets (PL 29831/0350). 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.

# 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 29831/0350) on 5th February 2009. The product is a prescription-only medicine.

This application was submitted as a simple abridged application according to Article 10c of EC Directive 2001/83, as amended, cross-referring to Alendronic Acid 70mg Tablets (PL 30306/0032), authorised to Actavis Ltd on 13th December 2007 as a change of ownership.

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

**LICENCE NO:** PL 29831/0350
**PROPRIETARY NAME:** Alendronic Acid 70mg Tablets
**ACTIVE(S):** Alendronic Acid
**COMPANY NAME:** Wockhardt UK Limited
**E.C. ARTICLE:** Article 10c (formerly Article 10.1(a)(i)) of Directive 2001/83/EC
**LEGAL STATUS:** POM

## 1. INTRODUCTION

This is a simple, informed consent application for Alendronic Acid 70mg Tablets submitted under Article 10c (formerly Article 10.1(a)(i)) of Directive 2001/83/EC.
The proposed MA holder is Wockhardt UK Limited, Ash Road North, Wrexham Industrial Estate, Wrexham, LL13 9UF, UK.
The application cross-refers to Alendronic Acid 70mg Tablets, granted to Actavis Group PTC EHF on 13th December 2007 as a change of ownership. The current application is considered valid.

## 2. MARKETING AUTHORISATION APPLICATION FORM

### 2.1 Name(s)

The proposed name of the product is Alendronic Acid 70mg Tablets. The product has been named in line with current requirements.

### 2.2 Strength, pharmaceutical form, route of administration, container and pack sizes

The product contains alendronic acid, equivalent to 70mg. It is to be stored in blisters composed of polyvinylchloride (PVC) and aluminium and is available in pack sizes of 2, 4 or 12 tablets. The proposed shelf-life (2 years) with no special precautions for storage conditions this is consistent with the details registered for the cross-reference product.

### 2.3 Legal status

On approval, the products will be available as prescription-only medicines (POM).

### 2.4 Marketing authorisation holder/Contact Persons/Company

Wockhardt UK Limited, Ash Road North, Wrexham Industrial Estate, Wrexham, LL13 9UF, UK.

**The QP responsible for pharmacovigilance is stated and CV is included.**

### 2.5 Manufacturers

The proposed manufacturing sites are consistent with those registered for the cross-reference product and evidence of GMP compliance has been provided.

### 2.6 Qualitative and quantitative composition

The proposed composition is consistent with the details registered for the cross-reference product.

### 2.7 Manufacturing process
The proposed manufacturing process is consistent with the details registered for the cross-reference product and the maximum batch size is stated.

### 2.8 Finished product/shelf-life specification
The proposed finished product specification is in line with the details registered for the cross-reference product.

### 2.9 Drug substance specification
The proposed drug substance specification is consistent with the details registered for the cross-reference product.

### 2.10 TSE Compliance
No materials of animal or human origin are included in the product. This is consistent with the cross-reference product.

## 3. EXPERT REPORTS
The applicant has included detailed expert reports in Module 2 of the application. Signed declarations and copies of the experts' CVs are enclosed in Module 1.4 for the quality, non-clinical and clinical experts. All are considered to have sufficient experience for their responsibilities.

## 4. PRODUCT NAME & APPEARANCE
See 2.1 for details of the proposed product name. The appearance of the product is identical to the cross-reference product.

## 5. SUMMARY OF PRODUCT CHARACTERISTICS
The proposed summary is consistent with the details registered for the cross-reference product.

## 6. PATIENT INFORMATION LEAFLET/CARTON

PIL
The patient information leaflet has been prepared in-line with the details registered for the cross-reference product.
No user testing has provided as the proposed PIL is identical to the reference product. This is acceptable in this instance.

Carton and blister
The proposed artwork is comparable to the artwork registered for the cross-reference product and complies with statutory requirements. In line with current legislation the applicant has also included the name of the product in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.

## 7. CONCLUSIONS
The data submitted with the application are acceptable. A Marketing Authorisation should be granted.

# PRECLINICAL ASSESSMENT

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

# CLINICAL ASSESSMENT

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

# OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

## QUALITY

The important quality characteristics of Alendronic Acid 70mg Tablets 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

Alendronic Acid 70mg Tablets is a well known drug and has been used in the treatment or prevention of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures. This application is identical to previously granted application for Alendronic Acid 70mg Tablets (PL 30306/0032), authorised to Actavis Ltd on 13th December 2007 as a change of ownership.

No new or unexpected safety concerns arise from this application.

## PRODUCT LITERATURE

The approved SmPC, PIL, technical leaflet, and labelling are satisfactory and consistent with that of the already approved strength of alendronic acid.

The approved labelling artwork complies with statutory requirements.

## RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with alendronic acid is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit is, therefore, considered to be positive.

# ALENDRONIC ACID 70MG TABLETS

# PL 29831/0350

## STEPS TAKEN FOR ASSESMENT

| | |
|---|---|
| 1 | The MHRA received the marketing authorisation applications on 12th January 2009. |
| 2 | Following standard checks and communication with the applicant the MHRA considered the applications valid on 27th January 2009. |
| 3 | The application was determined on 5th February 2009. |

# ALENDRONIC ACID 70MG TABLETS

# PL 29831/0350

## STEPS TAKEN AFTER AUTHORISATION - SUMMARY

| Date submitted | Application type | Scope | Outcome |
|---|---|---|---|
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |

# ALENDRONIC ACID 70MG TABLETS

# PL 29831/0350

## 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 cellecatose 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 corticosteriods. 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, corticosteriods, 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 ≥1% in either treatment group in the one-year study, or in ≥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 weeekly (n = 519) % | Alendronic Acid 10 mg/day (n = 370) % | Alendronic Acid 10 mg/day (n = 196) % | Placebo (n = 397) % |
| | | | | |
| *Gastro-intestinal* | | | | |
| 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 |
| *Musculoskeletal* | | | | |
| musculoskeletal (bone, | 2.9 | 3.2 | 4.1 | 2.5 |
| muscle or joint) pain | | | | |
| muscle cramp | 0.2 | 1.1 | 0.0 | 1.0 |
| | | | | |
| *Neurological* | | | | |
| 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 (≥ 10%),
common (≥ 1% and < 10%),
uncommon (≥ 0.1% and < 1%),

rare (≥ 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 ≤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/aluminium blisters in packs containing 2, 4 or 12 tablets.

**6.6 Special Precautions For Disposal**
No special requirements.

**7 MARKETING AUTHORISATION HOLDER**
Wockhardt UK Ltd
Ash Road North
Wrexham
LL13 9UF
UK

**8 MARKETING AUTHORISATION NUMBER(S)**
PL 29831/0350

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
05/02/2009

**10 DATE OF REVISION OF THE TEXT**
05/02/2009

# ALENDRONIC ACID 70MG TABLETS
# PL 29831/0350

# PATIENT INFORMATION LEAFLET

**Alendronic Acid 70mg Tablets**

**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.

**Index**


## 1 What Alendronic Acid tablets are and what they are used for

They are part of a group of drugs known as 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.

## 2 Before you take

**Do not take** Alendronic Acid tablets and **tell** your doctor if you:
- are **allergic** (hypersensitive) to alendronic acid or any of the other ingredients (see section 6).
- have certain **disorders of the oesophagus** (sometimes called the gullet, it is the tube that connects your mouth with your stomach)
- are **unable to stand or sit upright** for at least 30 minutes
- doctor has told you that you have **low blood calcium**
- are or think you may be **pregnant**
- are **breast-feeding**.

**Alendronic acid should not be given to children.**

**Check with your doctor or pharmacist** before taking Alendronic Acid tablets if you:
- suffer from **kidney** problems
- have any **allergies**
- have any **swallowing or digestive problems**

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

**Pregnancy and breast-feeding**
Alendronic Acid tablets must not be taken during pregnancy or while breast-feeding. If you are pregnant, planning to become pregnant or are breast-feeding ask your doctor or pharmacist for advice before taking any medicine.

**Sugar intolerance**
If you have been told you have an intolerance to some sugars, contact your doctor before taking this medicine, as it contains a type of sugar called lactose.

**3 How to take**
Always take Alendronic Acid tablets exactly as your doctor has told you. If you are not sure, check with your doctor or pharmacist.

One Alendronic Acid tablet is to be taken once a week.
Choose a day of the week to take your tablet that best fits with your normal schedule. After getting up for the day and before taking your first food, beverage or other medicine, **swallow** your Alendronic Acid 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 tablet, wait at least 30 minutes 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 take more than you should**
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.

**If you forget to take the tablets**
If you forget to take a dose of Alendronic acid take the missed tablet the morning after you remember. You should then continue with your weekly schedule using your chosen day. Do not take a double dose to make up for a forgotten dose.

**If you stop taking the tablets**
It is important that you continue taking Alendronic acid for as long as your doctor prescribes the medicine.
**Talk to your doctor** before you stop taking the tablets and follow their advice.

**4 Possible side effects**
Like all medicines, Alendronic Acid tablets can cause side effects, although not everybody gets them.

**Contact your doctor at once** if you experience any of the following:
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.

**Tell your doctor if you notice any of the following side effects** or notice any other effects not listed:
• **Common** (occurs in less than 1 in 10 users):
- headache, difficulty swallowing, tightening of the stomach muscles, and bone, muscle or joint pain
- stomach/abdominal pain, acid indigestion (heartburn), constipation, diarrhoea, indigestion, flatulence, feeling full or bloated, ulceration of the oesophagus (the tube that connects your mouth with your stomach),

• **Uncommon** (occurs in less than 1 in 100 users):
- nausea, vomiting, inflammation of the oesophagus, ulceration of the oesophagus, black and/or bloody stools
- rash, itching and redness of the skin

• **Rare** (occurs in less than 1 in 1,000 users):
- rash occasionally made worse by sunlight, inflammation or pain in the eye, also of the iris, low blood calcium levels

- transient flu-like symptoms (muscle weakness, a general feeling of illness and in rare cases fever) normally in relation to the beginning of treatment
- symptoms such as stomach ulcer, some severe, with haemorrhage have been seen but it is unclear if this is related to Alendronic Acid tablets
- mouth ulcers have occurred when the tablets have been chewed or sucked

• **Very rare** (occurs in less than 1 in 10,000 users):
- isolated cases of severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported.

If you notice any side effects, they get worse, or if you notice any not listed, please tell your doctor or pharmacist.

**5 How to store**
Keep out of the reach and sight of children.
There are no special precautions for storage.
Do not use Alendronic Acid tablets after the expiry date stated on the pack. The expiry date refers to the last day of that month.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

**6 Further information**
**What Alendronic Acid tablets contain**
- The active substance (the ingredient that makes the tablet work) is alendronic acid 70mg (as sodium trihydrate)
- The other ingredients are Cellactose 80, croscarmellose sodium, colloidal anhydrous silica and magnesium stearate

**What Alendronic Acid tablets look like and contents of the pack**
Alendronic Acid tablets are white, round, biconvex tablets.

Pack sizes of 2, 4 and 12 tablets. Not all pack sizes may be marketed.

To listen to or request a copy of this leaflet in Braille, large print or audio please call, free of charge:

0800 198 5000 (UK Only)

Please be ready to give the following information:

| Product Name | **Reference Number** |
|---|---|
| Alendronic Acid 70mg Tablets | 29831/0350 |

This is a service provided by the Royal National Institute of Blind People.

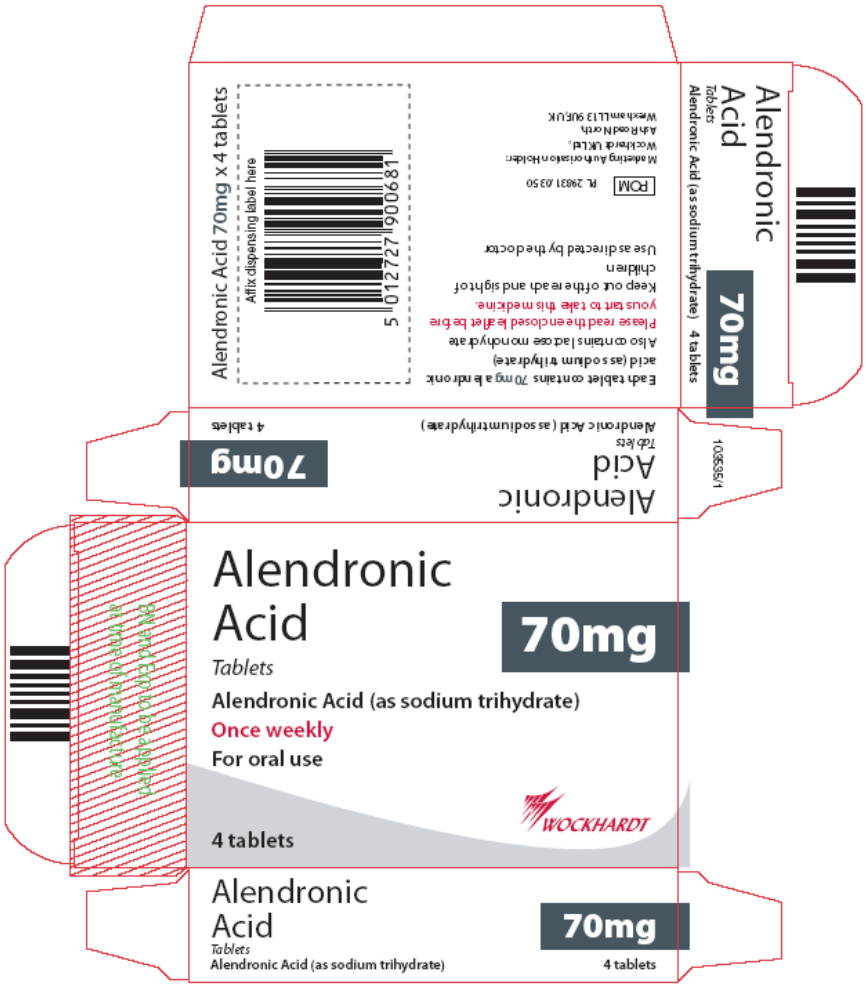
**Marketing Authorisation Holder**
Wockhardt UK Ltd, Ash Road North, Wrexham, LL13 9UF, UK

**Manufacturer:**
Actavis, Barnstable, EX32 8NS, UK.

Date of revision: November 2008

# ALENDRONIC ACID 70MG TABLETS
# PL 29831/0350
## LABELLING

## Carton




## Blister foil