

**Public Assessment Report**

**Decentralised Procedure**

**Alendronic Acid 10 mg Tablets**

**Alendronic Acid Once weekly 70 mg Tablets**

**PL 20075/0070-1**

**UK/H/1156/02-03/DC**

**Accord Healthcare Limited**

## **Lay summary**

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Accord Healthcare Limited Marketing Authorisations (licences) for the medicinal products Alendronic Acid 10 mg Tablets and Alendronic Acid Once weekly 70 mg Tablets (PL 20075/0070-1).

Alendronic acid belongs to a group of non-hormonal medicines called bisphosphonates. Alendronic acid prevents the loss of bone that occurs in men, post-menopausal women and patients receiving glucocorticoids, such as prednisolone and methylprednisolone. Alendronic acid has also been shown to help rebuild bone and make bone less likely to fracture in men and post-menopausal women with osteoporosis.

The data submitted in support of the applications for Alendronic Acid 10 mg Tablets and Alendronic Acid Once weekly 70 mg Tablets raised no clinically significant safety concerns and it was, therefore, judged that the benefits of using these products outweigh the risks; hence Marketing Authorisations have been granted.

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## Module 1

### Information about decentralised procedure

Name of the product in the Reference Member State	Alendronic Acid 10 mg Tablets Alendronic Acid Once weekly 70 mg Tablets
Name of the active substance (INN)	Sodium alendronate (alendronic acid)
Pharmacotherapeutic classification (ATC code)	Bisphosphonates (M05BA04)
Pharmaceutical form and strength	10 and 70 mg Tablets
Reference numbers for the Decentralised Procedure	UK/H/1156/02-03/DC
Reference Member State	United Kingdom
Member States concerned	AT, BE, CZ, DE, EE, IT, LT, LV, MT, NL, PL, RO, SE, SI, SK
Date of start of the procedure	3 September 2007
End date of decentralised procedure	28 August 2008
Marketing Authorisation Number	PL 20075/0070-1
Name and address of the authorisation holder	Accord Healthcare Limited Sage House 319, Pinner Road North Harrow Middlesex HA1 4 HF United Kingdom

## Module 2

### Summary of Product Characteristics

#### 1 NAME OF THE MEDICINAL PRODUCT

Alendronic Acid 10 mg Tablets

#### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10mg alendronic acid (as alendronate sodium)

Excipients: Each tablet contains 38.867 mg of Lactose Anhydrous

For a full list of excipients see section 6.1

#### 3 PHARMACEUTICAL FORM

Tablet

White to off-white, oval, biconvex tablet, debossed with '10' on one side and plain on other side.

#### 4 CLINICAL PARTICULARS

##### 4.1 Therapeutic indications

- Treatment of postmenopausal osteoporosis. Alendronic acid reduces the risk of vertebral and hip fractures.
- Treatment of osteoporosis in men at increased risk of fracture. A reduction in the incidence of vertebral, but not of non-vertebral fractures has been demonstrated.
- Prophylaxis of glucocorticoid-induced osteoporosis.

##### 4.2 Posology and method of administration

For oral use only.

Post-menopausal osteoporosis:

The recommended dosage is 10 mg once daily.

Osteoporosis in men:

The recommended dosage is 10 mg once daily.

Glucocorticoid-induced osteoporosis:

For post-menopausal women who are not receiving oestrogen treatment the recommended dose is one 10 mg tablet daily. For other populations, see summary of product characteristics for preparations that contain 5 mg alendronate.

To obtain satisfactory absorption of alendronate Alendronic acid tablets must be taken on an empty stomach immediately on rising in the morning, with plain water only, at least 30 minutes before the first food, drink or other medication of the day. Other drinks (including mineral water), food and some medicines are likely to reduce the absorption of alendronate (see section 4.5).

To assist delivery to the stomach and thus reduce the risk of irritation/side effects locally and in the oesophagus (see section 4.4)

- Alendronic acid tablets should only be swallowed on rising for the day with a whole glass of water (not less than 200 ml or 7 fl. oz).
  - Alendronic acid tablets should be swallowed whole. The tablets should not be chewed, sucked or allowed to dissolve in the mouth on account of the risk of oropharyngeal ulceration.
  - Patients should not lie down until after the first meal of the day, which must be at least 30 minutes after taking the tablet.
  - Patients should not lie down within 30 minutes of taking Alendronic acid tablets
  - Alendronic acid tablets should not be taken at bedtime or before arising for the day.
- Patients should be given a calcium and vitamin D supplement if the diet is inadequate (see section 4.4).

Use in elderly patients: In clinical trials there was no age-related difference with regard to efficacy or safety profiles of alendronate. Therefore no adjustment of the dose is necessary for elderly patients.

Use in impaired renal function

No dose adjustment is necessary in patients with a glomerular filtration rate (GFR) greater than 35 ml/min. Alendronate is not recommended for patients with impaired renal function if the GFR is less than 35 ml/min, as there is no experience of this.

Use in impaired hepatic function No dose adjustment is necessary.

Use in children Alendronic acid tablet is not recommended for use in children due to a lack of data on safety and efficacy.

### 4.3 Contraindications

Alendronic acid Tablet is contraindicated in:

- 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 excipient.
- Hypocalcaemia (see 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, or ulcers (see section 4.3).

Oesophageal reactions (sometimes severe and requiring hospitalisation), such as oesophagitis, oesophageal ulcers and oesophageal erosions, rarely followed by oesophageal stricture or perforation, 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 tablet properly and/or who continue to take alendronic acid tablet 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. However a causal relationship has not been established.

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 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, periodontal disease). 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.

Bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates. In post-marketing experience, these symptoms have rarely been severe and/or incapacitating (see section 4.8). The time to onset of symptoms varied from one day to several months after starting treatment. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.

Alendronic acid Tablet 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, ageing and glucocorticoid use 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.

Due to the 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 rare reports of symptomatic hypocalcaemia, which have occasionally 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 particularly important in patients receiving glucocorticoids.

#### Excipients

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

#### 4.5 Interaction with other medicinal products and other forms of interaction

If taken at the same time, it is likely that calcium supplements, antacids, and some oral medications will interfere with absorption of alendronic acid. Therefore, patients must wait at least 30 minutes after taking alendronic acid tablet before taking any other oral medication.

No other drug interactions of clinical significance are anticipated. Concomitant use of HRT (oestrogen ± progestin) and alendronic acid tablet was assessed in two clinical studies of one or two years duration in post-menopausal osteoporotic women (5.1). 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 drugs without evidence of clinical adverse interactions.

#### 4.6 Pregnancy and lactation

##### *Use during 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/fetal 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.

##### *Use during lactation*

It is not known whether alendronic acid tablet 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

Alendronic acid tablet has no effects on ability to drive and use machines.

#### 4.8 Undesirable effects

In a one-year study in post-menopausal women with osteoporosis the overall safety profiles of Alendronic acid 70 mg (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 tablet 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
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	Alendronic Acid Once Weekly 70 mg (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:

[Common ( $\geq 1/100$ ,  $< 1/10$ ), Uncommon ( $\geq 1/1000$ ,  $< 1/100$ ), Rare ( $\geq 1/10,000$ ,  $< 1/1000$ ), Very rare ( $< 1/10,000$  not known (cannot be estimated from the available data)]

**Immune system disorders:**

Rare: hypersensitivity reactions including urticaria and angioedema

**Metabolism and nutrition disorders:**

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

**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\*, melena

Rare: oesophageal stricture\*, oropharyngeal ulceration\*, upper gastro-intestinal PUBs (perforation, ulcers, bleeding)(see section 4.4)

\*See sections 4.2 and 4.4

Skin and subcutaneous tissue disorders:

Uncommon: rash, pruritus, erythema

Rare: rash with photosensitivity

Very rare and isolated cases: isolated cases of severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis

Musculoskeletal, connective tissue and bone disorders:

Common: musculoskeletal (bone, muscle or joint) pain

Rare: 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; severe musculoskeletal (bone, muscle or joint) pain (see 4.4 'Special warnings and precautions for use')

#### **General disorders and administration site conditions:**

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

During post-marketing experience the following reactions have been reported (frequency unknown):

**Nervous system disorders:** dizziness

**Ear and labyrinth disorders:** vertigo

**Musculoskeletal, connective tissue and bone disorders:** joint swelling

**General disorders and administration site conditions:** asthenia, peripheral oedema

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 tablet 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

No specific information is available on the treatment of overdosage with Alendronic acid. Hypocalcaemia, hypophosphataemia and upper gastro-intestinal adverse events, such as upset stomach, heartburn, oesophagitis, gastritis, or ulcer, may result from oral overdosage. 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: Drugs affecting bone structure and mineralisation, bisphosphonates.

ATC code: M05BA04

Alendronic acid is a bisphosphonate that inhibits osteoclastic bone resorption with no direct effect on bone formation. The bone formed during treatment with alendronic acid is of normal quality.

*Treatment of post-menopausal osteoporosis*

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 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: a three-year study of 2,027 patients who had at least one baseline vertebral (compression) fracture and a four-year study of 4,432 patients with low bone mass but without a baseline vertebral fracture, 37% of whom had osteoporosis as defined by a baseline femoral neck BMD at least 2.5 standard deviations below the mean for young, adult women. In all FIT patients with osteoporosis from both studies, alendronic acid reduced the incidence of: ≥ 1 vertebral fracture by 48%, multiple vertebral fractures by 87%, ≥1 painful vertebral fracture by 45%, any painful fracture by 31% and hip fracture by 54%.

Overall these results demonstrate the consistent effect of alendronic acid to reduce the incidence of fractures, including those of the spine and hip, which are the sites of osteoporotic fracture associated with the greatest morbidity.

#### *Concomitant use with oestrogen/hormone replacement therapy (HRT)*

The effects on BMD of treatment with alendronic acid tablet 10 mg once-daily and conjugated oestrogen (0.625 mg/day) either alone or in combination were assessed in a two-year study of hysterectomised, post-menopausal, osteoporotic women. At two years, the increases in lumbar spine BMD from baseline were significantly greater with the combination (8.3%) than with either oestrogen or alendronic acid tablet alone (both 6.0%). The effects on BMD when alendronic acid tablet was added to stable doses (for at least one year) of HRT (oestrogen ± progestin) were assessed in a one-year study in post-menopausal, osteoporotic women. The addition of alendronic acid tablet 10 mg once-daily to HRT produced, at one year, significantly greater increases in lumbar spine BMD (3.7%) vs. HRT alone (1.1%). In these studies, significant increases or favourable trends in BMD for combined therapy compared with HRT alone were seen at the total hip, femoral neck and trochanter. No significant effect was seen for total body BMD.

#### *Treatment of osteoporosis in men*

The efficacy of alendronic acid tablet 10 mg once daily in men (ages 31 to 87; mean, 63) with osteoporosis was demonstrated in a two-year study. At two years, the mean increases relative to placebo in BMD in men receiving alendronic acid tablet 10 mg/day were: lumbar spine, 5.3%; femoral neck, 2.6%; trochanter, 3.1%; and total body, 1.6%. Alendronic acid tablet was effective regardless of age, race, gonadal function, baseline rate of bone turnover, or baseline BMD. Consistent with much larger studies in post-menopausal women, in these 127 men, alendronic acid tablet 10 mg/day reduced the incidence of new vertebral fracture (assessed by quantitative radiography) relative to placebo (0.8% vs. 7.1%) and, correspondingly, also reduced height loss (-0.6 vs. -2.4 mm).

#### *Glucocorticoid-induced osteoporosis*

The efficacy of alendronic acid tablet 5 and 10 mg once daily in men and women receiving at least 7.5 mg/day of prednisone (or equivalent) was demonstrated in two studies. At two years of treatment, spine BMD increased by 3.7% and 5.0% (relative to placebo) with alendronic acid tablet 5 and 10 mg/day respectively. Significant increases in BMD were also observed at the femoral neck, trochanter, and total body. In post-menopausal women not receiving oestrogen, greater increases in lumbar spine and trochanter BMD were seen in those receiving 10 mg alendronic acid tablet than those receiving 5 mg. Alendronic acid tablet was effective regardless of dose or duration of glucocorticoid use. Data pooled from three dosage groups (5 or 10 mg for two years or 2.5 mg for one year followed by 10 mg for one year) showed a significant reduction in the incidence of patients with a new vertebral fracture at two years (Alendronic acid 0.7% vs. placebo 6.8%).

## **5.2 Pharmacokinetic properties**

### **Absorption**

Relative to an intravenous (IV) reference dose, the oral bioavailability of alendronic acid tablet in women was 0.7% for doses ranging from 5 to 40 mg when administered after an overnight fast and two hours before a standardised breakfast. Oral bioavailability in men (0.6%) was similar to that in women. Bioavailability was decreased similarly to an

estimated 0.46% and 0.39% when alendronic acid tablet was administered one hour or half an hour before a standardised breakfast. In osteoporosis studies, alendronic acid tablet was effective when administered at least 30 minutes before the first food or beverage of the day.

Bioavailability was negligible whether alendronic acid tablet 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 tablet transiently distributes to soft tissues following 1 mg/kg IV 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 IV dose of [<sup>14</sup>C] alendronic acid tablet, 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 IV dose, the renal clearance of alendronic acid tablet was 71 ml/min, and systemic clearance did not exceed 200 ml/min. Plasma concentrations fell by more than 95% within six hours following IV administration. The terminal half-life in humans is estimated to exceed ten years, reflecting release of alendronic acid from the skeleton. Alendronic acid tablet 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 drugs 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 IV 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 female 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 fetal ossification. The relevance to humans is unknown.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Lactose anhydrous  
Cellulose microcrystalline (E460)  
Croscarmellose sodium  
Magnesium stearate

### **6.2 Incompatibilities**

Not applicable

### **6.3 Shelf life**

2 years

### **6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions

### **6.5 Nature and contents of container**

Opaque white PVC/ALU blister  
Pack size: 28 tablets.

### **6.6 Special precautions for disposal**

Any unused product or waste material should be disposed of in accordance with local requirements.

## **7 MARKETING AUTHORISATION HOLDER**

Accord Healthcare Limited  
Sage House  
319, Pinner Road  
North Harrow  
Middlesex HA1 4 HF  
United Kingdom

## **8 MARKETING AUTHORISATION NUMBER(S)**

PL 20075/0070

## **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION**

26/09/2008

## **10 DATE OF REVISION OF THE TEXT**

26/09/2008

## **1 NAME OF THE MEDICINAL PRODUCT**

Alendronic Acid Once weekly 70 mg Tablets

## **2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

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

Excipients: Each tablet contains 272.070 mg of Lactose Anhydrous

For a full list of excipients see section 6.1

## **3 PHARMACEUTICAL FORM**

Tablet

White to off- white, oval, biconvex, tablet, debossed with 'AHI' on one side and plain on other side.

## **4 CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

Treatment of post-menopausal osteoporosis. Alendronic acid reduces the risk of vertebral and hip fractures.

### **4.2 Posology and method of administration**

The recommended dosage is one 70 mg tablet once weekly.

*To permit adequate absorption of alendronic acid:*

Alendronic acid Tablet 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 Tablet should only be swallowed upon arising for the day with a full glass of water (not less than 200 ml or 7 fluid ounce).
- Patients should not chew the tablet or allow the tablet to dissolve in their mouths because of a potential for oropharyngeal ulceration.
- Patients should not lie down until after their first food of the day which should be at least 30 minutes after taking the tablet.
- Patients should not lie down for at least 30 minutes after taking Alendronic acid.
- Alendronic acid Tablet 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 GFR greater than 35 ml/min. Alendronic acid Tablet is not recommended for patients with renal impairment where GFR is less than 35 ml/min, due to lack of experience.

*Use in children (under 18):* Alendronic acid has been studied in a small number of patients with osteogenesis imperfecta under 18 years of age. Results are insufficient to support its use in children

Alendronic acid Once Weekly 70 mg has not been investigated in the treatment of glucocorticoid-induced osteoporosis.

### **4.3 Contraindications**

Alendronic acid is contraindicated in:

- 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 excipient.
- Hypocalcaemia (see 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 tablet 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 or perforation, 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 tablet 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 tablet 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.

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 and corticosteroids. Osteonecrosis of the jaw has also been reported in patients with osteoporosis receiving oral bisphosphonates periodontal disease.



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, periodontal disease). 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.

Bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates. In post-marketing experience, these symptoms have rarely been severe and/or incapacitating (see section 4.8). The time to onset of symptoms varied from one day to several months after starting treatment. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.

Patients should be instructed that if they miss a dose of Alendronic acid once weekly tablet, 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 tablet 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, ageing and glucocorticoid use 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.

Due to the 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 rare reports of symptomatic hypocalcaemia, which have occasionally 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 particularly important in patients receiving glucocorticoids.

#### *Excipients*

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

## **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

##### *Use during 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.

##### *Use during lactation*

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

#### 4.7 Effects on ability to drive and use machines

Alendronic acid tablet has no effects on ability to drive and use machines.

#### 4.8 Undesirable effects

In a one-year study in post-menopausal women with osteoporosis the overall safety profiles of Alendronic acid tablet 70 mg (n=519) and alendronic acid tablet 10 mg/day (n=370) were similar.

In two three-year studies of virtually identical design, in post-menopausal women (alendronic acid tablet 10 mg: n=196, placebo: n=397) the overall safety profiles of alendronic acid tablet 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 tablet 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 Once Weekly 70 mg (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:

[Common ( $\geq 1/100$ ,  $< 1/10$ ), Uncommon ( $\geq 1/1000$ ,  $< 1/100$ ), Rare ( $\geq 1/10,000$ ,  $< 1/1000$ ), Very rare ( $< 1/10,000$  not known (cannot be estimated from the available data))]

**Immune system disorders:**

Rare: hypersensitivity reactions including urticaria and angioedema

**Metabolism and nutrition disorders:**

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

**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 distention, acid regurgitation

Uncommon: nausea, vomiting, gastritis, oesophagitis\*, oesophageal erosions\*, melena

Rare: oesophageal stricture\*, oropharyngeal ulceration\*, upper gastro-intestinal PUBs (perforation, ulcers, bleeding)(see section 4.4)

\*See sections 4.2 and 4.4

Skin and subcutaneous tissue disorders:

Uncommon: rash, pruritus, erythema

Rare: rash with photosensitivity

Very rare and isolated cases: isolated cases of severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis

Musculoskeletal, connective tissue and bone disorders:

Common: musculoskeletal (bone, muscle or joint) pain

Rare: 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; severe musculoskeletal (bone, muscle or joint) pain (see section 4.4)

#### **General disorders and administration site conditions:**

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

During post-marketing experience the following reactions have been reported (frequency unknown):

**Nervous system disorders - rare:** dizziness

**Ear and labyrinth disorders:** vertigo

**Musculoskeletal, connective tissue and bone disorders:** joint swelling

**General disorders and administration site conditions:** asthenia, peripheral oedema

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 tablet 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 tablet. 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

ATC Code: M05B A04

#### *Pharmacotherapeutic group:*

Drugs affecting bone structure and mineralisation, bisphosphonates. The active ingredient of 'Alendronic acid Tablets', alendronate sodium, 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 Tablets' 70 mg (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 tablet 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  $\geq 1$

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  $\geq 1$  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 tablet 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 tablet was administered one hour or half an hour before a standardised breakfast. In osteoporosis studies, alendronic acid tablet 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 tablet 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 tablet (a mean increase ranging from 20% to 44%).

### *Distribution*

Studies in rats show that alendronic acid tablet 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 [ $^{14}\text{C}$ ] alendronic acid tablet, 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 tablet 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 tablet 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 female rats have shown that treatment with alendronic acid tablet 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 fetal ossification. The relevance to humans is unknown.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Lactose anhydrous  
Cellulose microcrystalline (E460)  
Croscarmellose sodium  
Magnesium stearate

### **6.2 Incompatibilities**

Not applicable

### **6.3 Shelf life**

2 years

### **6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions

### **6.5 Nature and contents of container**

OPA-AL-PVC/Al blister  
Pack size: 4 tablets.

### **6.6 Special precautions for disposal**

Any unused product or waste material should be disposed of in accordance with local requirements.

## **7 MARKETING AUTHORISATION HOLDER**

Accord Healthcare Limited  
Sage House  
319, Pinner Road

North Harrow  
Middlesex HA1 4 HF  
United Kingdom

- 8      MARKETING AUTHORISATION NUMBER(S)**  
PL 20075/0071
- 9      DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**  
26/09/2008
- 10     DATE OF REVISION OF THE TEXT**  
26/09/2008



## **Module 3**

### **Product Information Leaflet**

## PACKAGE LEAFLET: INFORMATION FOR THE USER

### Alendronic Acid 10 mg Tablets

(Alendronic Acid)

**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 or pharmacist.

#### **In this leaflet:**

1. What Alendronic Acid Tablets is and what it is used for
2. Before you take Alendronic Acid Tablets
3. How to take Alendronic Acid Tablets
4. Possible side effects
5. How to store Alendronic Acid Tablets
6. Further information

#### **1. What Alendronic Acid Tablets is and what it is used for**

Alendronic Acid belongs to a group of non-hormonal medicines called bisphosphonates. Alendronic Acid prevents the loss of bone that occurs in men, post-menopausal women and patients receiving glucocorticoids such as prednisolone and methylprednisolone. Alendronic Acid also has been shown to help rebuild bone and makes bone less likely to fracture in post-menopausal women and men with osteoporosis.

##### **What is Alendronic Acid Tablets used for**

Your doctor has prescribed alendronic acid because you either have osteoporosis or you are at risk of developing this disease. Osteoporosis is a thinning and weakening of the bones. It is common in women after the menopause. The menopause occurs when the ovaries stop producing the female hormone, oestrogen or they are removed. Oestrogen helps to keep a woman's skeleton healthy. Following the menopause, bone loss occurs and bones become weaker. The earlier a woman reaches the menopause, the greater the risk of osteoporosis. Osteoporosis can also occur in men due to a number of causes including ageing and/or a low level of the male hormone, testosterone. In all instances, bone is removed faster than it is formed, so bone loss occurs and bones become weaker. A class of steroid hormones (Corticosteroids) can also cause bone loss and osteoporosis in both sexes.

Early on, osteoporosis usually has no symptoms. If left untreated, however, it can result in fractures (broken bones). Although fractures usually cause pain, fractures of the bones of the spine may go unnoticed until they cause height loss.

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

##### *How can osteoporosis be treated/prevented?*

It is important to remember that if you already have osteoporosis that it can be treated and that it is never too late to begin.

Your doctor has prescribed these tablets to treat your osteoporosis or to prevent you from developing this disease. Alendronic acid not only prevents the loss of bone but actually helps to rebuild bone you may have lost and make bone less likely to fracture. In addition to your treatment with alendronic acid, your doctor may recommend that you make some changes to your lifestyle, which may help your condition. These are:

- Stopping smoking:* Smoking appears to increase the rate at which you lose bone and, therefore, 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.
- Eating 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 Tablets**

##### **Do not take Alendronic Acid Tablets**

- If you have certain disorders of the oesophagus (sometimes called the gullet and is the tube that connects your mouth with your stomach)
- If you are unable to stand or sit upright for at least 30 minutes
- If you are allergic (hypersensitive) to alendronic acid or any of the other ingredients of alendronic acid
- If your doctor has told you that you have low blood calcium

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

##### **Take special care with Alendronic Acid Tablets**

It is important to tell your doctor before taking Alendronic Acid Tablets

- If you suffer from kidney problems

- If you have any allergies
- If you have any swallowing or digestive problems
- If you have low blood calcium
- If you have gum disease
- If you have a planned dental extraction

A dental examination should be considered before you start treatment with alendronic acid tablets if you have any of the conditions below.

- You have cancer
- You don't receive routine dental care
- You are undergoing chemotherapy or radiotherapy
- You are taking steroids
- You have gum disease

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

### **Taking other medicines**

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

This medicine can interact with other medication which you take by mouth, and it is important that you follow the advice given under the heading 'How to take Alendronic Acid Tablets'.

### **Taking Alendronic Acid Tablets with food and drink**

This medicine can interact with food and drink, and it is important that you follow the advice given in 'How to take Alendronic Acid Tablets'

### **Pregnancy and breast-feeding**

You should not take alendronic acid tablets if you are or think you may be pregnant, or if you are breast-feeding. Ask your doctor or pharmacist for advice before taking any medicine

### **Driving and using machines**

Alendronic Acid Tablets should not affect your ability to drive or use machines.

### **Important information about some of the ingredients of Alendronic Acid Tablets**

Alendronic Acid Tablets contains 0.039 g of lactose. When taken according to the dosage recommendations each dose supplies up to 0.039 g of lactose. If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicinal product. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

## **3. How to take Alendronic Acid Tablets**

Always take alendronic acid tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

You should do the following to help make sure you will benefit from alendronic acid tablets. *It is very important that you follow actions 1, 2, 3 and 4 to help the tablet reach your stomach quickly and help reduce potential for irritation of your oesophagus (the tube that connects your mouth with your stomach).*

1. After getting up for the day, swallow your alendronic acid tablets with a full glass of plain water only (not less than 200 ml or 7 fluid ounce). – not mineral water– not coffee or tea– not juice
2. After swallowing your alendronic acid tablets do not lie down - stay fully upright (sitting or standing) for at least 30 minutes and until after your first food of the day. Do not chew or allow the tablet to dissolve in your mouth.
3. Do not take alendronic acid tablets at bedtime or before getting up for the day.
4. If you develop difficulty or pain upon swallowing, chest pain, or new or worsening heartburn, stop taking alendronic acid tablets and contact your doctor.
5. After swallowing your 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 Tablets is effective only if taken when your stomach is empty.
6. You must take alendronic acid tablets exactly as your doctor has told you. It is important that you continue taking alendronic acid tablets for as long as your doctor prescribes the medicine. How much alendronic acid tablets you need to take will depend on why you are taking it and what other drugs you are taking.

### **If you take more Alendronic Acid Tablets than you should**

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

### **If you forget to take Alendronic Acid Tablets**

If you miss a dose, do not take an extra tablet to make up, just carry on with the next dose as normal.

### **If you stop taking Alendronic Acid Tablets**

It is important that you continue taking alendronic acid tablets for as long as your doctor prescribes the medicine. Alendronic Acid Tablets can treat your osteoporosis only if you continue to take the tablets.

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

#### **4. Possible side effects**

Like all medicines, alendronic acid tablets can cause side effects, although not everybody gets them.

Most patients do not have side effects from taking these tablets; however, as with any medicine, they may have unintended or undesirable effects.

The following terms are used to describe how often side effects have been reported.

Very Common side effects (equal or more than 1 out of 10 patients)

Common side effects (less than 1 out of 10 but more than 1 out of 100 people),

Uncommon side effects (less than 1 out of 100 but equal or more than 1 out of 1,000 patients),

Rare side effects (less than 1 out of 1000 but equal or more than 1 out of 10,000 patients),

Very rare side effects (less than 1 out of 10,000 patients)

##### **Common side effects (less than 1 out of 10 but more than 1 out of 100 people):**

- heartburn;
- difficulty swallowing;
- pain upon swallowing;
- ulceration of the gullet (oesophagus - the tube that connects your mouth with your stomach) which can cause chest pain,
- bone, muscle and/or joint pain
- abdominal pain;
- uncomfortable feeling in the stomach or belching after eating;
- constipation;
- full or bloated feeling in the stomach;
- diarrhoea;
- flatulence;
- headache

##### **Uncommon side effects less than 1 out of 100 but equal or more than 1 out of 1,000 patients):**

- nausea;
- vomiting
- irritation or inflammation of the gullet (oesophagus - the tube that connects your mouth with your stomach) or stomach
- black or tar-like stools
- rash;
- itching;
- redness of the skin

##### **Rare side effects (less than 1 out of 1000 but equal or more than 1 out of 10,000 patients):**

- allergic reactions such as hives; swelling of the face, lips, tongue and/or throat, possibly causing difficulty breathing or swallowing
- symptoms of low blood calcium levels including muscle cramps or spasms and/or tingling sensation in the fingers or around the mouth
- stomach or peptic ulcers (sometimes severe or with bleeding)
- narrowing of the gullet (oesophagus - the tube that connects your mouth with your stomach)
- jaw problems associated with delayed healing and infection, often following tooth extraction
- blurred vision, pain or redness in the eye
- rash made worse by sunlight
- severe bone, muscle and/or joint pain
- mouth ulcers when the tablets have been chewed or sucked
- transient flu-like symptoms, such as aching muscles, generally feeling unwell and sometimes with fever usually at the start of treatment

##### **Very rare side effects (less than 1 out of 10,000 patients):**

- severe skin reactions

Tell your doctor or pharmacist promptly about these or any other unusual symptoms. It will help if you make a note of what you experienced, when it started and how long it lasted.

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

#### **5. How to store Alendronic Acid Tablets**

- Keep out of reach and sight of children.
- Do not use alendronic acid tablets after the expiry date, which is stated on the carton and blister after 'EXP'. The expiry date refers to the last day of that month.
- This medicinal product does not require any special storage conditions
- Medicine 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 contains:**

The active substance is alendronic acid (as sodium alendronate).

Each tablet contains 10mg alendronic acid (as alendronate sodium)

The other ingredients are lactose anhydrous, cellulose microcrystalline (E460), croscarmellose sodium and magnesium stearate.

### **What Alendronic Acid Tablets looks like and content of the pack:**

Alendronic Acid 10 mg Tablets are available as white to off-white, oval, biconvex tablet, debossed with '10' on one side and plain on other side.

Alendronic Acid 10 mg Tablets are available in opaque white PVC/ALU blister packs containing 28 tablets.

### **Marketing Authorisation Holder and Manufacturer :**

Accord Healthcare Limited  
Sage House , 319 Pinner Road,  
North Harrow,  
Middlesex HA1 4HF,  
UK

The leaflet was last approved in September 2008

## PACKAGE LEAFLET: INFORMATION FOR THE USER

### Alendronic Acid Once weekly 70 mg Tablets (Alendronic Acid)

**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 or pharmacist.

**In this leaflet:**

1. What Alendronic Acid Tablets is and what it is used for
2. Before you take Alendronic Acid Tablets
3. How to take Alendronic Acid Tablets
4. Possible side effects
5. How to store Alendronic Acid Tablets
6. Further information

#### 1. What Alendronic Acid Tablets is and what it is used for

Alendronic acid belongs to a group of non-hormonal medicines called bisphosphonates. Alendronic acid prevents the loss of bone that occurs in women after they have been through the menopause, and helps to rebuild bone. Alendronic acid reduces the risk of spine and hip fractures.

##### What is Alendronic Acid Tablets used for?

Your doctor has prescribed alendronic acid tablets because you have a disease called osteoporosis. Osteoporosis is a thinning and weakening of the bones. It is common in women after the menopause. At the menopause, the 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 the menopause, the greater the risk of osteoporosis. Early on, osteoporosis usually has no symptoms. If left untreated, however, it can result in fractures (broken bones). Although fractures usually cause pain, fractures of the bones of the spine may go unnoticed until they cause height loss. Fractures (broken bones) may occur during normal everyday activity, such as lifting, or from minor injury that would not be sufficient to fracture normal bone. Fractures (broken bones) usually occur at the hip, spine, or wrist and can lead not only to pain but also to considerable deformity (problem) and disability (such as stooped posture, or 'dowager's hump', and loss of mobility).

##### How can osteoporosis be treated/prevented?

Osteoporosis can be treated and it is never too late to begin treatment. Alendronic acid Tablet not only prevents the loss of bone but actually helps to rebuild bone you may have lost and reduces the risk of bones breaking in the spine and hip.

As well as your treatment with Alendronic acid Tablet, your doctor may suggest you make changes to your lifestyle to help your condition, such as:

- Stopping smoking:* Smoking appears to increase the rate at which you lose bone and, therefore, may increase your risk of fracture.
- Exercise:* Like muscles, bones need exercise to stay strong and healthy. Consult your doctor before you begin an exercise programme.
- Eating 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 Tablets

##### Do not take Alendronic Acid Tablets

- If you have certain disorders of the oesophagus (sometimes called the gullet and is the tube that connects your mouth with your stomach)
- If you are unable to stand or sit upright for at least 30 minutes
- If you are allergic (hypersensitive) to alendronic acid or any of the other ingredients of alendronic acid
- If your doctor has told you that you have low blood calcium

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

##### Take special care with Alendronic Acid Tablets

It is important to tell your doctor before taking Alendronic Acid Tablets

- If you suffer from kidney problems
- If you have any allergies
- If you have any swallowing or digestive problems
- If you have low blood calcium
- If you have gum disease
- If you have a planned dental extraction

A dental examination should be considered before you start treatment with Alendronic Acid Tablets if you have any of the conditions below.

- You have cancer

- You don't receive routine dental care
- You are undergoing chemotherapy or radiotherapy
- You are taking steroids
- You have gum disease

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

Irritation, inflammation or ulceration of the gullet (oesophagus – the tube that connects your mouth with your stomach) often with symptoms of chest pain, heartburn, or difficulty or pain upon swallowing may occur, especially if patients do not drink a full glass of water and/or if they lie down less than 30 minutes after taking Alendronic Acid Tablets. These side effects may worsen if patients continue to take Alendronic Acid Tablets after developing these symptoms.

#### **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.

It is likely that calcium supplements, antacids, and some oral medicines will interfere with the absorption of Alendronic acid Tablets if taken at the same time. Therefore, it is important that you follow the advice given under the heading HOW TO TAKE ALENDRONIC ACID TABLETS.

#### **Taking Alendronic Acid Tablets with food and drink**

It is likely that food and beverages (including mineral water) will make Alendronic acid Tablets less effective if taken at the same time. Therefore, it is important that you follow the advice given in heading HOW TO TAKE ALENDRONIC ACID TABLETS.

#### **Children and adolescents**

Alendronic acid Tablets should not be given to children and adolescents.

#### **Pregnancy and breast-feeding:**

You should not take alendronic acid tablets if you are or think you may be pregnant, or if you are breast-feeding.

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

#### **Driving and using machines**

Alendronic acid tablets should not affect your ability to drive or use machines.

#### **Important information about some of the ingredients of Alendronic Acid Tablets**

Alendronic Acid Tablets contains 0.272 g of lactose. When taken according to the dosage recommendations each dose supplies up to 0.272 g of lactose. If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicinal product. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

### **3. How to take Alendronic Acid Tablets**

#### **Take one Alendronic Acid Tablet once a week.**

Follow these instructions carefully to make sure you will benefit from alendronic acid.

1) Choose the day of the week that best fits your schedule. Every week, take one alendronic acid tablet on your chosen day.

*It is very important to follow instructions 2), 3), 4) and 5) to help the alendronic acid tablet reach your stomach quickly and help reduce the chance of irritating your gullet (oesophagus - the tube that connects your mouth with your stomach).*

2) After getting up for the day and before taking any food, drink, or other medicine, swallow your alendronic acid tablet with a full glass of water only (not mineral water) (not less than 200 ml or 7 fluid ounce).

- 1 • Do not take with mineral water (still or sparkling).
- 2 • Do not take with coffee or tea.
- 3 • Do not take with juice or milk.

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

3) Do not lie down — stay fully upright (sitting, standing or walking) — for at least 30 minutes after swallowing the tablet. Do not lie down until after your first food of the day.

4) Do not take alendronic acid bedtime or before getting up for the day.

5) If you develop difficulty or pain upon swallowing, chest pain, or new or worsening heartburn, stop taking alendronic acid and contact your doctor.

6) After swallowing your alendronic acid tablet, wait at least 30 minutes before taking your first food, drink, or other medicine 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 Alendronic Acid Tablets than you should**

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

#### **If you forget to take Alendronic Acid Tablets**

If you miss a dose, just take one Alendronic Acid Tablets 70 mg on the morning after you remember. Do not take two tablets on the same day. Return taking one tablet once a week, as originally scheduled on your chosen day.

#### **If you stop taking Alendronic Acid Tablets**

It is important that you continue taking Alendronic Acid Tablets for as long as your doctor prescribes the medicine. Alendronic Acid Tablets can treat your osteoporosis only if you continue to take the tablets.

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

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#### **4. Possible side effects**

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Like all medicines, alendronic acid tablets can cause side effects, although not everybody gets them.

Most patients do not have side effects from taking these tablets; however, as with any medicine, they may have unintended or undesirable effects.

The following terms are used to describe how often side effects have been reported.

Very Common side effects (equal or more than 1 out of 10 patients)

Common side effects (less than 1 out of 10 but more than 1 out of 100 people),

Uncommon side effects (less than 1 out of 100 but equal or more than 1 out of 1,000 patients),

Rare side effects (less than 1 out of 1000 but equal or more than 1 out of 10,000 patients),

Very rare side effects (less than 1 out of 10,000 patients)

##### **Common side effects (less than 1 out of 10 but more than 1 out of 100 people):**

- heartburn;
- difficulty swallowing;
- pain upon swallowing;
- ulceration of the gullet (oesophagus - the tube that connects your mouth with your stomach) which can cause chest pain,
- bone, muscle and/or joint pain
- abdominal pain;
- uncomfortable feeling in the stomach or belching after eating;
- constipation;
- full or bloated feeling in the stomach;
- diarrhoea;
- flatulence;
- headache

##### **Uncommon side effects (less than 1 out of 100 but equal or more than 1 out of 1,000 patients):**

- nausea;
- vomiting
- irritation or inflammation of the gullet (oesophagus – the tube that connects your mouth with your stomach) or stomach
- black or tar-like stools
- rash;
- itching;
- redness of the skin

##### **Rare side effects (less than 1 out of 1000 but equal or more than 1 out of 10,000 patients):**

- allergic reactions such as hives; swelling of the face, lips, tongue and/or throat, possibly causing difficulty breathing or swallowing
- symptoms of low blood calcium levels including muscle cramps or spasms and/or tingling sensation in the fingers or around the mouth
- stomach or peptic ulcers (sometimes severe or with bleeding)
- narrowing of the gullet (oesophagus – the tube that connects your mouth with your stomach)
- jaw problems associated with delayed healing and infection, often following tooth extraction
- blurred vision, pain or redness in the eye
- rash made worse by sunlight
- severe bone, muscle and/or joint pain
- mouth ulcers when the tablets have been chewed or sucked
- transient flu-like symptoms, such as aching muscles, generally feeling unwell and sometimes with fever usually at the start of treatment

##### **Very rare side effects (less than 1 out of 10,000 patients):**

- severe skin reactions

During post-marketing experience the following side effects have been reported (frequency unknown):

- dizziness
- joint swelling
- tiredness
- swelling in the hands or legs



Laboratory test findings:

Very common: mild and transient decreases in blood calcium and phosphate levels, generally within the normal range.

Tell your doctor or pharmacist promptly about these or any other unusual symptoms. It will help if you make a note of what you experienced, when it started and how long it lasted.

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

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#### **5. How to store Alendronic Acid Tablets**

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- Keep out of reach and sight of children.
- This medicinal product does not require any special storage conditions
- Do not take the tablets after the 'EXP', which is clearly marked on the carton, and blister. The expiry date refers to the last day of that month.
- Medicine 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.

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#### **6. Further information**

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##### **What Alendronic Acid Tablets contains**

The active substance is alendronic acid (as sodium alendronate).

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

The other ingredients are lactose anhydrous, cellulose microcrystalline (E460), croscarmellose sodium and magnesium stearate.

##### **What Alendronic Acid Tablets looks like and content of the pack:**

Alendronic Acid 70 mg Tablets are available as white to off-white, oval, biconvex tablet debossed with 'AHI' on one side and plain on other side.

Alendronic Acid 70 mg Tablets are available in OPA-Al-PVC/Al blister packs containing 4 tablets.

##### **Marketing Authorisation Holder and Manufacturer :**

Accord Healthcare Limited  
Sage House , 319 Pinner Road,  
North Harrow, Middlesex  
HA1 4HF,  
UK

The leaflet was last approved in September 2008

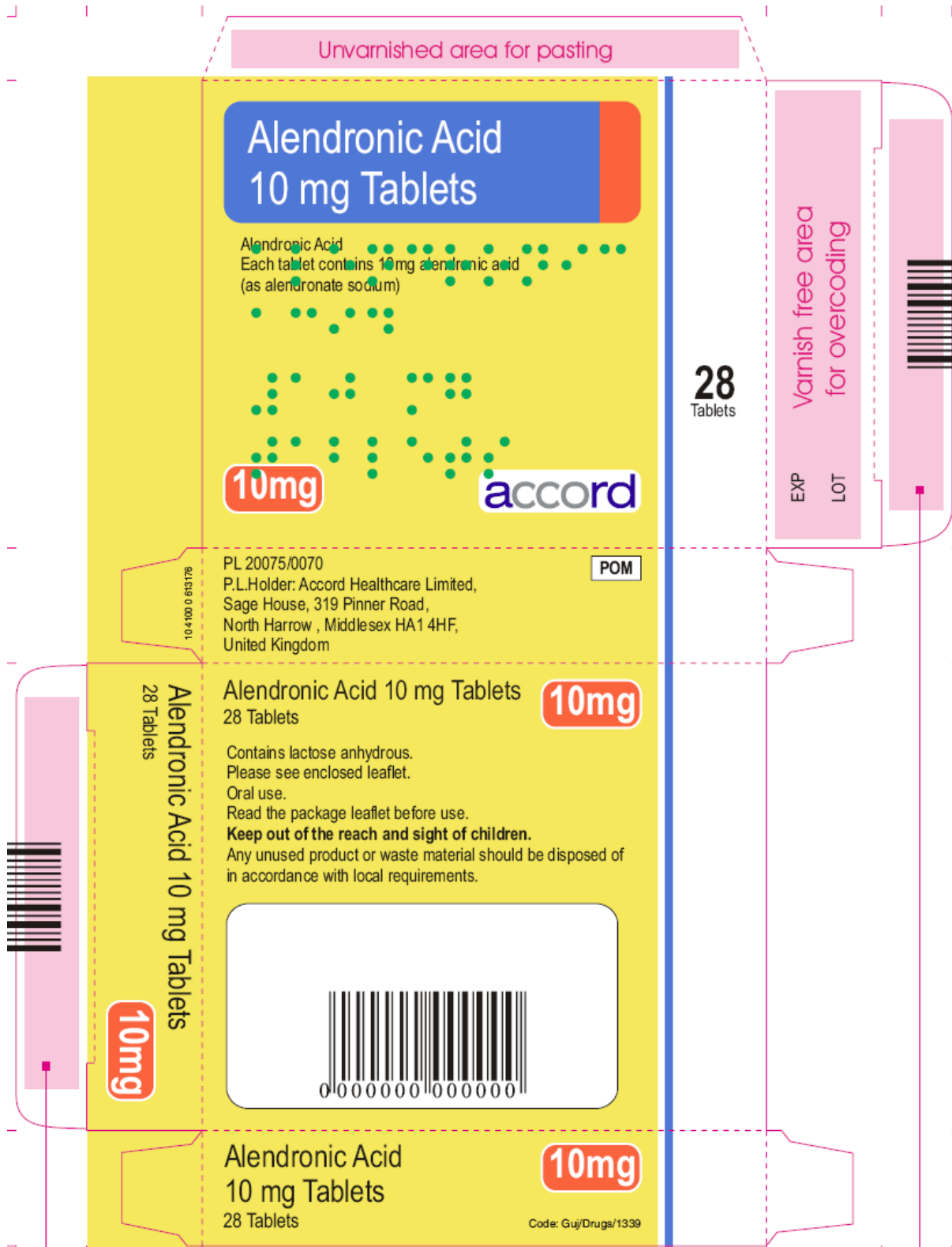
## Module 4

### Labelling

Label:



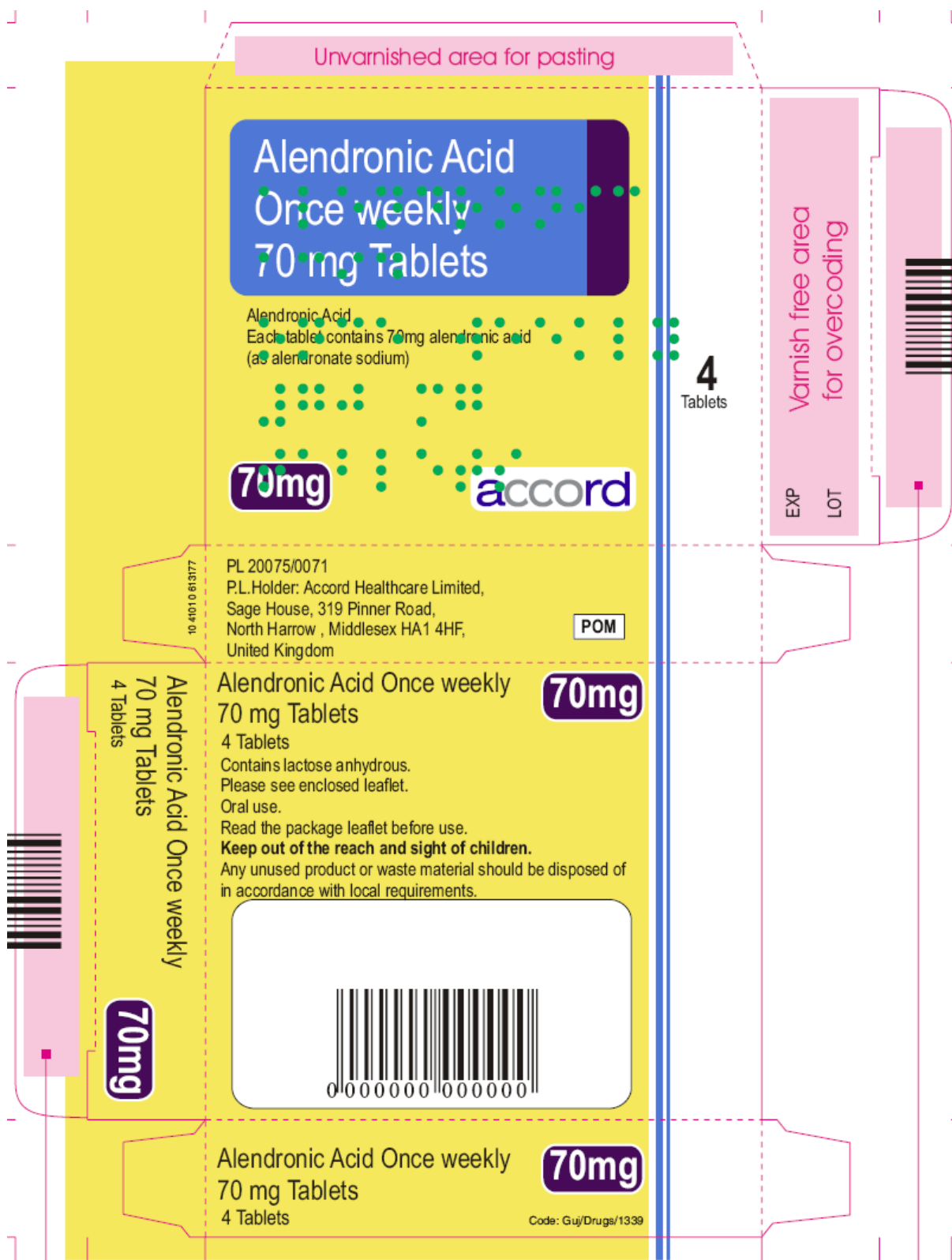
**Carton:**



**Label:**



**Carton:**



## Module 5

### Scientific discussion during initial procedure

#### RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Alendronic Acid 10 mg Tablets and Alendronic Acid Once weekly 70 mg Tablets in the treatment or prevention of osteoporosis could be approved.

#### EXECUTIVE SUMMARY

##### Problem statement

These applications have been submitted under Article 10(1) of Directive 2001/83/EC, as amended. The products are claimed to be generic to reference products that have been authorised in the EEA for over 10 years and the application is considered valid.

With the UK as the Reference Member State in this Decentralised Procedure, Accord Healthcare Limited applied for a Marketing Authorisations for Alendronic Acid 10 mg Tablets and Alendronic Acid Once weekly 70 mg Tablets in Austria, Belgium, the Czech Republic, Germany, Estonia, Italy, Lithuania, Latvia, Malta, the Netherlands, Poland, Romania, Sweden, Slovenia and the Slovak Republic.

##### About the product

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

Alendronic Acid has been used for the proposed indications for many years.

##### General comments on the submitted dossier

The dossier submitted was of reasonable quality.

##### General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those non-Community sites.

The applicant has given an undertaking that the bioequivalence study was conducted in compliance with the GLP and GCP.

## SCIENTIFIC OVERVIEW AND DISCUSSION

### Quality aspects

#### Active substance

The control tests and specifications for the active substance are adequately drawn up and are in line with the Ph. Eur. The quality of the active substance is assured by the supporting Ph. Eur. Certificate of Suitability.

#### Drug Product

The development of the product has been described, the choice of excipients is justified and their functions explained. The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed and the results show that the finished products meet the specifications proposed.

The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up.

The proposed shelf-life of 2 years with no special storage conditions for the drug product is considered acceptable.

#### Non-clinical aspects

Specific non-clinical studies have not been performed, which is acceptable for this application for a generic product. The non-clinical overview provides an adequate review of the known pharmacological, pharmacokinetic and toxicological properties of alendronate sodium.

#### Clinical aspects

No new efficacy and safety data were submitted and none is required for this type of application.

The applicant has provided biowaver justification for the 10 mg strength tablets. This is acceptable. Bioequivalence data from studies using the higher strength 70 mg formulation can be extrapolated to the lower strength.

#### Pharmacokinetics

An open label, balanced, randomized, two-treatment, two-sequence, two-period, single dose, crossover oral bioequivalence was carried out on healthy, adult, male subjects.

The test (alendronate sodium 70 mg tablets) and the reference (Fosamex 70 mg) products were administered under fasting conditions. The results were as follows:-

**Table1 : Summary of the results (Subjects No. = 86)**

<b>Parameters</b>	<b>Test (Alendronate sodium)</b> (mean $\pm$ sd)	<b>Reference (Fosamax)</b> (mean $\pm$ sd)
Ae <sub>0-t</sub> (ng)	622760.2 (396848.5)	676782.5 (40811.2)
R <sub>max</sub> (ng/h)	190477.3 (120623.3)	207962.5 (120943.7)
T <sub>max</sub> (h)	1.28 (0.46)	1.24 (0.48)
T <sub>max</sub> * (h)	1.5 (0.88)	1.5 (0.88)

\*Medians and interquartile ranges

**Table 2: Alendronate Sodium (A) vs Fosamax® (B)**

	<b>Ae<sub>0-t</sub> (ng)</b>	<b>R<sub>max</sub> (ng/h)</b>
Ratio <sup>1</sup>	93.53%	90.67%
90 % Geometric C.I, <sup>2</sup>	83.32% to 104.98%	80.92% to 101.60%
Intra-subject CV	48.02%	47.19%

<sup>1</sup> Calculated using least-squares means

<sup>2</sup> 90% Geometric Confidence Interval using In-transformed data

Based on the above data, bioequivalence of the test product with the reference product has been shown.

### **BENEFIT RISK ASSESSMENT**

The risk: benefit ratio for this product is considered favourable and approval is recommended.



## **Overall conclusion**

### **QUALITY**

The important quality characteristics of Alendronic Acid 10 mg Tablets and Alendronic Acid Once weekly 70 mg 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 preclinical data is needed for these applications.

No new or unexpected safety concerns arise from these applications.

### **EFFICACY**

Clinical studies have demonstrated the efficacy of alendronate sodium in the prevention and treatment of osteoporosis.

The product literature is satisfactory and consistent with that for the innovator product.

### **RISK BENEFIT ASSESSMENT**

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified.