Public Assessment Report

Decentralised Procedure

Alendronic acid 70 mg Tablets
UK/H/1921/01/DC

UK licence no: PL 08553/0358

Dr. Reddy’s Laboratories (UK) Limited
LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Dr Reddy’s Laboratories (UK) Limited a Marketing Authorisation (licence) for the medicinal product Alendronic acid 70 mg Tablets (PL 08553/0358) on 15th October 2009. 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 these applications 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.
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## Module 1

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Alendronic acid 70 mg Tablets</th>
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<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10.1</td>
</tr>
<tr>
<td><strong>Active Substance</strong></td>
<td>Alendronate sodium trihydrate (Alendronic acid)</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Tablet</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>70 mg</td>
</tr>
<tr>
<td><strong>MA Holder</strong></td>
<td>Dr. Reddy’s Laboratories (UK) Limited</td>
</tr>
<tr>
<td><strong>RMS</strong></td>
<td>UK</td>
</tr>
<tr>
<td><strong>CMS</strong></td>
<td>Austria, Bulgaria, Spain, Italy, Portugal and Romania</td>
</tr>
<tr>
<td><strong>Procedure Number</strong></td>
<td>UK/H/1921/01/DC</td>
</tr>
<tr>
<td><strong>End of Procedure</strong></td>
<td>23rd September 2009</td>
</tr>
</tbody>
</table>
Module 2  
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT  
Alendronic acid 70 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION  
Each tablet contains 70 mg alendronic acid (as alendronate sodium trihydrate).  
For excipients, see 6.1.

3 PHARMACEUTICAL FORM  
Tablet  
White to off-white, oval, biconvex, uncoated tablet debossed ‘RDY’ on one side and ‘70’ on the other side.

4 CLINICAL PARTICULARS  
4.1 Therapeutic indications  
Treatment of postmenopausal 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 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 also section 4.5).

To facilitate delivery to the stomach and thus reduce the potential for local and oesophageal irritation/adverse experiences (see also section 4.4):
• Alendronic acid should only be swallowed upon arising for the day with a full glass of water (not less than 200 ml).
• 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 tablet.
• Alendronic acid 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 also 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 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 70mg 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 gastrointestinal 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 gastrointestinal problems, such as dysphagia, oesophageal disease, gastritis, duodenitis, ulcers, or with a recent history (within the previous year) of major gastrointestinal disease such as peptic ulcer, or active gastrointestinal bleeding, or surgery of the upper gastrointestinal tract other than pyloroplasty (see also 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 also 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.

Alendronic acid is not recommended for patients with renal impairment where GFR is less than 35 ml/min, (see also 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 also section 4.3). Other disorders of 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 70mg.

Due to the positive effects of alendronic acid to increase bone mineral, small, asymptomatic decreases in serum calcium and phosphate may occur, especially in patients receiving glucocorticoids, in whom calcium absorption may be decreased.

Ensuring adequate calcium and vitamin D intake is therefore particularly important in patients receiving glucocorticoids.

Osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection (including osteomyelitis), has been reported in patients with cancer who are 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, and 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 also 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 treatment. A subset had recurrence of symptoms when rechallenged with the same medicinal product or another bisphosphonate.

Stress fractures (also known as insufficiency fractures) of the proximal femoral shaft have been reported in patients treated long-term with alendronic acid (time to onset in the majority of cases ranged from 18 months to 10 years). The fractures occurred after minimal or no trauma and some patients experienced thigh pain, often associated with imaging features of stress fractures, weeks to months before presenting with a completed femoral fracture. Fractures were often bilateral; therefore the contralateral femur should be examined in bisphosphonate-treated patients who have sustained a femoral shaft fracture. Poor healing of these fractures was also reported. Discontinuation of bisphosphonate therapy in patients with stress fracture is advisable pending evaluation of the patient, based on an individual benefit risk assessment.

Patients should be instructed that if they miss a dose of Alendronic acid 70mg, 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.

### 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 also 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 with alendronic acid 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 hypocalcaemia (see also 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 should not be used by breast-feeding women.

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

There is no data existing to indicate that alendronic acid affects a patient's ability to drive or operate 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 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:

<table>
<thead>
<tr>
<th></th>
<th>One-Year Study</th>
<th>Three-Year Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alendronic acid</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Once Weekly 70mg (n = 519) %</td>
<td>10mg /day (n = 370) %</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>abdominal pain</td>
<td>3.7</td>
<td>3.0</td>
</tr>
<tr>
<td>dyspepsia</td>
<td>2.7</td>
<td>2.2</td>
</tr>
<tr>
<td>acid regurgitation</td>
<td>1.9</td>
<td>2.4</td>
</tr>
<tr>
<td>nausea</td>
<td>1.9</td>
<td>2.4</td>
</tr>
<tr>
<td>abdominal distention</td>
<td>1.0</td>
<td>1.4</td>
</tr>
<tr>
<td>constipation</td>
<td>0.8</td>
<td>1.6</td>
</tr>
<tr>
<td>diarrhoea</td>
<td>0.6</td>
<td>0.5</td>
</tr>
<tr>
<td>dysphagia</td>
<td>0.4</td>
<td>0.5</td>
</tr>
<tr>
<td>flatulence</td>
<td>0.4</td>
<td>1.6</td>
</tr>
<tr>
<td>gastritis</td>
<td>0.2</td>
<td>1.1</td>
</tr>
<tr>
<td>gastric ulcer</td>
<td>0.0</td>
<td>1.1</td>
</tr>
<tr>
<td>oesophageal ulcer</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td><strong>Musculoskeletal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>musculoskeletal (bone, muscle or joint) pain</td>
<td>2.9</td>
<td>3.2</td>
</tr>
<tr>
<td>muscle cramp</td>
<td>0.2</td>
<td>1.1</td>
</tr>
<tr>
<td><strong>Neurological</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>headache</td>
<td>0.4</td>
<td>0.3</td>
</tr>
</tbody>
</table>

The following adverse experiences have also been reported during clinical studies and/or post-marketing use:

*Common (≥ 1/100, < 1/10), Uncommon (≥ 1/1,000, <1/100), Rare (≥ 1/10,000, < 1/1,000), Very Rare (< 1/10,000)*

**Immune system disorders:**
Rare: hypersensitivity reactions including urticaria and angioedema

**Metabolism and nutrition disorders:**
Rare: symptomatic hypocalcaemia, often in association with predisposing conditions. (see also section 4.4)

**Nervous system disorders:**
Common: headache

**Eye disorders:**
Rare: uveitis, scleritis, episcleritis

**Gastrointestinal 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) (see section 4.4).

*See also sections 4.2 and 4.4

Skin and subcutaneous tissue disorders:
Uncommon: rash, pruritus, erythema

Rare: rash with photosensitivity

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

Musculoskeletal and connective tissue 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 (see also section 4.4); joint swelling, severe musculoskeletal (bone, muscle or joint) pain (see also section 4.4)

Frequency not known: Stress fractures of the proximal femoral shaft (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: 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 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 gastrointestinal adverse events, such as upset stomach, heartburn, oesophagitis, gastritis, or ulcer, may result from oral overdose. No specific information is available on the treatment of overdose 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: M05BA04

The active ingredient of (tablet name), alendronic acid, 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 (n=519) and alendronic acid 10 mg daily (n=370) was demonstrated in a one-year multicentre study of postmenopausal 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 (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.

Fracture Intervention Trial 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):

Fracture Intervention Trial 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%).

Fracture Intervention Trial 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 also 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. Foetuses from rats given high doses showed an increased incidence of incomplete ossification. The relevance to humans is unknown.

6 **PHARMACEUTICAL PARTICULARS**

6.1 **List of excipients**
- Microcrystalline Cellulose
- Povidone K30
- Croscarmellose Sodium
- Magnesium Stearate

6.2 **Incompatibilities**
Not applicable.

6.3 **Shelf life**
2 years

6.4 **Special precautions for storage**
No special storage condition.

6.5 **Nature and contents of container**
Tablets are available in Alu/Alu blister packs of 4, 12, 24, and 28 tablets.

Components of Alu/Alu pack:
Cold formable foil as the forming material and hard tempered aluminium foil as the lidding foil.

6.6 **Special precautions for disposal**
No special requirements.

7 **MARKETING AUTHORISATION HOLDER**
Dr. Reddy’s Laboratories (UK) Ltd.
6 Riverview Road
Beverley
HU17 0LD
UK
8  MARKETING AUTHORISATION NUMBER(S)
   PL08553/0358

9  DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
   15/10/2009

10 DATE OF REVISION OF THE TEXT
    15/10/2009
Module 3
PATIENT INFORMATION LEAFLET

Package Leaflet: Information for the User
ALENDRONIC ACID 70 MG TABLETS
(Alenontric acid an alendronate sodium trihydrate)

Once Weekly Tablet

Read all of this leaflet carefully before you start taking this medicine, even if
this is a repeat prescription.

- 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.
- It is particularly important to understand the information in section 1, before
  taking this medicine.

In this leaflet:
1. What Alendronic acid 70mg Tablets are and what they are used for
2. Before you take Alendronic acid 70mg Tablets
3. How to take
4. Possible side effects
5. How to store
6. Further information

1. What Alendronic acid 70mg Tablets are and what they are used for

Alendronic acid Tablets contain alendronic acid which belongs to a group of
non-steroidal medicines called bisphosphonates. Alendronic acid 70mg Tablets are used to

- prevent bone loss that occurs in women after they have been through the
  menopause known as post-menopausal osteoporosis
- treat post-menopausal osteoporosis by helping bones become stronger
- reduce the risk of spine and hip fractures.

2. Before you take Alendronic acid 70mg Tablets

Do not take Alendronic acid 70mg Tablets if you

- are allergic (hypersensitive) to alendronate sodium trihydrate or to any
  of the other ingredients in the tablets (see section 4).
- have difficulty swallowing because of problems with your oesophagus
  (the tube that connects your mouth with your stomach)
- cannot stand or sit up right for at least 30 minutes
- have low blood calcium.

Check with your doctor before taking Alendronic acid 70mg Tablets if you have

- pain in your gums
- upper gastrointestinal problems such as oesophageal disease, inflammation of the lining of the stomach, stomach or gastric ulcers or gastrinomas or gastrooesophageal reflux
- peptic ulcer
- planned dental extraction.

Dental examination
Some people taking bisphosphonate drugs like Alendronic acid develop jaw problems
due to delayed healing and infection after a tooth extraction. If possible, you should
avoid having dental surgery whilst taking Alendronic acid and a dental examination is
recommended before you start treatment if you

- have cancer
- are having chemotherapy or radiotherapy
- are taking steroids
- do not receive regular dental care
- have gum disease.

Taking other medicines

Please tell your doctor or pharmacist before taking Alendronic acid 70mg Tablets if you
are taking or have recently taken any other medicines, including those bought
without a prescription and herbal remedies.

If taken at the same time, calcium supplements, antacids, and some oral
corticosteroids are likely to interfere with the absorption of Alendronic acid 70mg Tablets.
Therefore it is important not to take any other medicines for at least 30
minutes before or after taking Alendronic acid.

Pregnancy and breast-feeding

Alendronic acid 70mg Tablets are not intended for use by women who have been
through the menopause. You should not take Alendronic acid 70mg Tablets if you are
or think you may be pregnant, or if you are breast-feeding.

Driving and using machines

Alendronic acid 70mg Tablets should not affect your ability to drive or operate
machines.

3. How to take

Take

Take one Alendronic acid 70mg Tablet once a week. Choose the day of the week
that best fits your schedule. Every week, take one tablet on your chosen day.

When to take

Food and other medicines can interfere with the absorption of Alendronic acid tablets and the tablets only work if taken when your stomach is empty.

Therefore take the tablet after getting up for the day before having any food, drinks, or
other medicines. Wait at least 30 minutes before taking your first food, drink or
other medicine of the day, including antacids, calcium, supplements and vitamins.

How to take

Swallow the tablet with a full glass of water (not less than 250 ml).

Do not take with

- mineral water (still or sparkling)
- coffee or tea
- juices or milk.

Other important instructions

Alendronic acid can cause irritation, inflammation and ulcers of the oesophagus (the
tube that connects your mouth with your stomach). To avoid this,

1. Do not chew the tablet or allow it to dissolve in your mouth.
2. 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.
3. Do not take the tablet at bedtime or before getting up for the day.

If you develop any sign of oesophageal irritation after swallowing the tablet, such as
difficulty or pain on swallowing, heartburn or pain in your chest, stop taking the tablets
and contact your doctor.
If you take more than you should
If you take too many tablets by mistake, drink a full glass of milk and contact your doctor immediately. Do not try to make yourself vomit and do not lie down.

If you forget to take your tablet
If you miss a dose, just take one tablet on the morning after you remember. Skip the dose if the next dose is due in the next couple of days. Do not take two tablets on the same day. Return to taking one tablet once a week, as originally scheduled on your chosen day.

If you stop taking the tablets
It is important to carry on taking Alendronic acid 70mg Tablets for as long as your doctor prescribed. Alendronic acid 70mg Tablets can only work if you consistently take them.

4. Possible side effects
Like all medicines, Alendronic acid 70mg Tablets can cause side effects, although not everybody gets them.

Tell your doctor or pharmacist if you have any of the following side effects or any other unusual effects.

Common (occur in less than 1 in 10 patients):
- difficulty swallowing
- oesophageal ulcers causing difficulty or pain upon swallowing, heartburn or chest pain
- bone, muscle and/or joint pain
- abdominal pain, uncomfortable feeling in the stomach or bloating after eating, full or bloated feeling in the stomach, flatulence (wind), acid regurgitation
- constipation, diarrhoea
- headache

Uncommon (occur in less than 1 in 100 patients):
- feeling sick (nausea), being sick (vomiting)
- irritation or inflammation of the oesophagus (the tube that connects your mouth with your stomach) causing difficulty or pain upon swallowing, heartburn or chest pain
- inflammation of the stomach (gastroenteritis)
- black or tea-like stools
- rash, itching, redness of the skin

Rare (occur in less than 1 in 10,000 patients):
- allergic reactions such as itchy skin rash (rash), swelling of the face, lips, tongue and/or throat, possibly causing difficulty breathing or swelling
- 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 oesophagus (the tube that connects your mouth with your stomach)
- jaw problems due to delayed healing and infection (often after 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
- periods of flu-like symptoms, such as aching muscles, generally feeling unwell and sometimes with fever (usually at the start of treatment).

Very rare (occur in less than 1 in 100,000 patients):
- severe skin reactions such as peeling, blistering of the skin.

Frequency unknown: fracture of the thigh bone in patients on long-term treatment with Alendronic acid 70mg Tablets. Thigh pain, weakness or discomfort may be an early indication of a possible fracture of the thigh bone.

5. How to store
Keep out of the reach and sight of children. This product does not require any special storage conditions.

Do not use after the expiry date.

Do not remove the tablets from the blister pack until you are ready to take the medicine.

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 70mg Tablets contain
The active substance which makes the tablets work is alendronic acid. Each tablet contains 70 mg alendronic acid as alendronate sodium hydrate.

The other ingredients are microcrystalline cellulose, croscarmellose sodium, povidone K30 and magnesium stearate.

What Alendronic acid 70mg Tablets look like and contents of the pack
Alendronic acid 70mg Tablets are available as white to off-white, oval, licorice-shaped uncoated tablets marked “70” on one side and “70” on the other side.

Alendronic acid 70mg Tablets are available in the blister pack of 4, 12, 34, and 28.

Not all pack sizes may be available.

Mastering Authentication Holder and Manufacturer
Dr Reddy’s Laboratories Ltd, 8 Kichenow Road, Beverley, HU17 0LD
Alendronic acid 70mg Tablets P: 08453030398
This leaflet was last updated in June 2009.
Module 4
Labelling
Alendronic acid 70 mg Tablets

Once weekly tablet

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN

REPACKED BY: Dr. Reddy's Laboratories Ltd.

For onward supply to:

Dr. Reddy's Laboratories Ltd.

Office Address: 6th Floor, Building 125, Dr. Reddy's Tech Park,

No. 1, Nizam Marg, Gachibowli, Hyderabad 500032, India

Mumbai Office: 1st Floor, Building 256, Dr. Reddy's Tech Park,

No. 2, Nizam Marg, Gachibowli, Hyderabad 500032, India

Telephone: 8000808800

For onward supply to:

Dr. Reddy's Laboratories Ltd.

Office Address: 6th Floor, Building 125, Dr. Reddy's Tech Park,

No. 1, Nizam Marg, Gachibowli, Hyderabad 500032, India

Mumbai Office: 1st Floor, Building 256, Dr. Reddy's Tech Park,

No. 2, Nizam Marg, Gachibowli, Hyderabad 500032, India

Telephone: 8000808800

Each tablet contains 70 mg of alendronic acid as alendronic acid monohydrate.

Take as directed by a medical practitioner.

Read the package leaflet before use.

Alendronic acid 70 mg Tablets

Once weekly tablet

24 Tablets

Alendronic acid 70 mg Tablets

Once weekly tablet

24 Tablets

Alendronic acid 70 mg Tablets

Once weekly tablet

24 Tablets

Alendronic acid 70 mg Tablets

Once weekly tablet

24 Tablets
Blister foil

- Alendronic acid 70mg Tablets
  Dr. Reddy's Laboratories (UK) Ltd
- Alendronic acid 70mg Tablets
  Dr. Reddy's Laboratories (UK) Ltd
- Alendronic acid 70mg Tablets
  Dr. Reddy's Laboratories (UK) Ltd
- Alendronic acid 70mg Tablets
  Dr. Reddy's Laboratories (UK) Ltd
- Alendronic acid 70mg Tablets
  Dr. Reddy's Laboratories (UK) Ltd
- Alendronic acid 70mg Tablets
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- Alendronic acid 70mg Tablets
  Dr. Reddy's Laboratories (UK) Ltd
- Alendronic acid 70mg Tablets
  Dr. Reddy's Laboratories (UK) Ltd
- Alendronic acid 70mg Tablets
  Dr. Reddy's Laboratories (UK) Ltd
Module 5
Scientific discussion during initial procedure

I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the RMS considers that the application by Dr. Reddy’s Laboratories (UK) Limited for Alendronic acid 70 mg Tablets for the treatment of post-menopausal osteoporosis, is approvable.

This application is made under Article 10.1 of 2001/83 EC, as amended. Alendronic acid 70 mg Tablets, has been shown to be a generic medicinal product of Fosamax® 70mg Tablets (PL 0025/0399) which was granted to Merck Sharp and Dohme Ltd in the UK on 7th February 2000. The reference medicinal product authorised for not less than 10 years is Fosamax® 10mg Tablets (Merck Sharp and Dohme Ltd, licensed in the UK on 28th July 1995, over 10 years ago.

The active substance alendronic acid is a bisphosphonate which inhibits osteoclastic bone resorption. The original product is listed as Fosamax 5mg tablet which was licensed in July 1993 in Italy. Fosamax 10mg tablets were then licensed for use in the UK on 28th July 1995 (PL 00025/0326) for the treatment of post-menopausal osteoporosis. In 2000 the indication was extended to include the treatment of osteoporosis in men. A UK marketing authorisation was then granted for the use of Fosamax® 70 mg tablets once weekly (PL 00025/0399) for the treatment of post-menopausal osteoporosis on 10th November 2000. The reference drug for that license was Fosamax 10mg Tablets (PL 00025/0326).

Alendronic acid is a potent inhibitor of osteoclast-mediated bone resorption. It is indicated for the treatment or prevention of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures.

The oral absorption of alendronic acid is limited under fasting conditions (<2%) and negligible in the presence of food. The ultimate site of sequestration is the bone, especially osteoclasts. Alendronic acid decreases bone turnover leading to progressive gains in bone mass. Alendronic acid is pharmacologically inactive when incorporated in bone matrix.

The active ingredient alendronic acid is a bisphosphonate that inhibits osteoclastic bone resorption with no direct effect on bone formation. Preclinical studies have shown preferential localization of alendronic acid 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 alendronic acid is of normal quality.

Osteoporosis remains the leading cause of bone fracture and associated morbidity in postmenopausal women today. Basically osteoporosis is a loss of bone mass and its aetiology involves genetic, environmental, hormonal and nutritional factors.

No new preclinical or clinical studies were conducted and none are required for an application of this type.

The RMS has been assured that acceptable standards of GMP are in place for this product type at all sites responsible for the manufacture, batch release 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 (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS has been reassured that the submitted bioequivalence study has been carried out in accordance with GCP, and agreed ethical principles.

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

The RMS considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The marketing authorisation holder has provided adequate justification for not submitting a risk management plan (RMP).

II.  ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Alendronic acid 70mg Tablets |
| Name(s) of the active substance(s) (INN) | Alendronate sodium trihydrate (Alendronic acid) |
| Pharmacotherapeutic classification (ATC code) | Bisphosphonates (M05B A04) |
| Pharmaceutical form and strength(s) | Tablets, 70mg |
| Reference numbers for the Mutual Recognition Procedure | UK/H/1921/01/DC |
| Reference Member State | United Kingdom |
| Member States concerned | Austria, Bulgaria, Spain, Italy, Portugal and Romania |
| Marketing Authorisation Number(s) | PL 08553/0358 |
| Name and address of the authorisation holder | Dr. Reddy’s Laboratories (UK) Limited, 6 Riverview Road, Beverley, East Yorkshire, HU17 0LD, United Kingdom. |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

Nomenclature:

INN: Alendronic acid

Chemical name: (4-amino-1-hydroxybutylidene)bisphosphonic acid monosodium salt trihydrate or α-hydroxy-δ-amino butylidene diphosphonic acid, monosodium salt, trihydrate or Sodium trihydrogen (4-amino-1-hydroxy butylidene) diphosphonate, trihydrate

Structure:

![Structure Diagram]

3H₂O

Molecular formula
C₆H₁₂NNaO₇P₂·3H₂O

Molecular weight
325.1

General Properties
A white or almost white crystalline powder, soluble in water, practically insoluble in methanol and in methylene chloride. Mono-crystalline structure.

Solubility
Soluble in water, practically insoluble in methanol and in methylene chloride. Mono-crystalline structure.

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

The active substance alendronic acid is subject of a Ph.Eur monograph. An appropriate specification is provided for the active substance alendronic acid. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Active alendronic acid is stored in appropriate packaging that comply with Directive 2002/72/EC (as amended), and are suitable for contact with foodstuffs. Specifications and certificates of analysis have been provided.
Batch analysis data are provided and comply with the proposed specification. Satisfactory certificates of analysis have been provided for standards used by the active substance manufacturer during validation studies.

Appropriate stability data have been generated for drug substance stored in the same immediate packaging as the commercial packaging. The data demonstrates the stability of the drug substance and supports an appropriate retest period when stored in the proposed packaging.

P. Medicinal Product

Other Ingredients
Other ingredients consist of pharmaceutical excipients namely microcrystalline cellulose, povidone K30, croscarmellose sodium and magnesium stearate. All ingredients used comply with their relevant Ph.Eur monographs. Satisfactory certificates of analysis have been provided for all excipients.

Pharmaceutical Development
The formulation objective was to develop generic tablets bioequivalent to the reference product, Fosamax 70mg Tablets.

The objectives of the development programme were to develop a formula and a manufacturing process for Alendronic acid 70 mg Tablets, to produce tablets with the following:

1) comparable dissolution profile to the brand
2) bioequivalent to the brand
3) meet all physical and chemical specifications for the dosage form in general and for this product.

Dissolution and impurity profiles
Dissolution and impurity profiles of the drug product were found to be similar to those for the reference product.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process.

Finished Product Specification
The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided for three pilot scale batches and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container-Closure System
Alendronic acid 70 mg Tablets are packaged in blister packs composed of aluminium. Blister pack presentation is available in pack sizes of 4, 12, 24 and 28 tablets. All primary product packaging complies with EU legislation regarding contact with food.

Stability of the product
Stability studies have been performed on the three pilot-scale batches which are satisfactory. A commitment has been provided that stability studies will be performed on the first three commercial scale batches of the product.
All batches are packaged in the proposed commercial packaging. Stability testing is performed according to the relevant ICH guidelines. Based on the results of the stability studies, the applicant has proposed a shelf life of 2 years, with no specific storage conditions which is acceptable.

**SPC, PIL, Labels**
The SPC, PIL and Labels are pharmaceutically acceptable.

**Conclusion**
The grant of a marketing authorisation is recommended.

### III.2 PRE-CLINICAL ASPECTS

The pharmacodynamic, pharmacokinetic and toxicological properties of alendronic acid are well known. As alendronic acid is a well known active substance, no further studies are required and the applicant has provided none. An overview based on the literature is thus appropriate.

The non-clinical overview has been written by a suitably qualified person. The overview, dated May 2008, refers to a total of 108 references from the published literature. The overview is acceptable in view of the fact that the toxicological properties of alendronic acid are well known.

Section 5.3 of the SPC is acceptable.

The marketing authorisation holder has provided adequate justification for not submitting an Environmental Risk Assessment.

There are no objections to the approval of Alendronic acid 70 mg tablets from a non-clinical point of view.

### III.3 CLINICAL ASPECTS

**Introduction**
Alendronic acid is a potent inhibitor of osteoclast-mediated bone resorption. It is indicated for the treatment or prevention of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures.

The oral absorption of alendronic acid is limited under fasting conditions (<2%) and negligible in the presence of food. The ultimate site of sequestration is the bone, especially osteoclasts. Alendronic acid decreases bone turnover leading to progressive gains in bone mass. Alendronic acid is pharmacologically inactive when incorporated in bone matrix.

The active ingredient Alendronic acid is a bisphosphonate that inhibits osteoclastic bone resorption with no direct effect on bone formation. Preclinical studies have shown preferential localization of alendronic acid 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 alendronic acid is of normal quality.

Osteoporosis remains the leading cause of bone fracture and associated morbidity in postmenopausal women today. Basically osteoporosis is a loss of bone mass and its aetiology involves genetic, environmental, hormonal and nutritional factors.
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.

Alendronic acid has been available as a 10 mg tablet (Fosamax®, MSD) for daily treatment of osteoporosis for over 10 years. More recently, a once weekly 70 mg tablet of alendronic acid has become available, which retains all the therapeutic benefits of the lower dose tablet, but makes dosing and compliance issues far simpler for patients, since therapy is long-term.

**Indication**

“Treatment of postmenopausal osteoporosis. Alendronic acid reduces the risk of vertebral and hip fractures”.

**Posology**

The recommended dosage is one 70 mg tablet once weekly.

*To permit adequate absorption of alendronic acid:*

Alendronic acid 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 also section 4.5 of SPC).

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

- Alendronic acid should only be swallowed upon arising for the day with a full glass of water (not less than 200 ml).
- 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 tablet.
- Alendronic acid 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 also section 4.4 of SPC).

**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 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 70mg has not been investigated in the treatment of glucocorticoid-induced osteoporosis.

**Assessor's comment:**

*Both the Indications and Posology are in line with those for the innovator product Fosamax.*
The application contains an adequate review of published clinical data. No new pharmacodynamic or clinical data were submitted for this application and none were required. Regarding safety, no serious or unexpected adverse events were identified in the expert report.

The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

**Clinical study reports**

To support the application, the applicant has submitted as report one single dose bioequivalence study, using plasma data.

**Biowaiver**

N/A

**Pharmacokinetic studies**

One single dose bioequivalence study was submitted, comparing the Alendronate (Alendronic acid) 70 mg test formulation and reference Fosamax 70 mg tablet.

**Title:** An Open Label, Balanced, Randomized, Two-Treatment, Two-Period, Two-Sequence, Single Dose, Crossover, Bioequivalence Study of Alendronate sodium 70 mg Tablets of Dr. Reddy’s Laboratories Limited, comparing with that of FOSAMAX 70 mg Tablets of Merck, UK in healthy adult human subjects Under Fasting Conditions

**Assessor's comment:**

This single dose bioequivalence study is sufficient to support the current application.

**Methods**

**Study design**

This was a randomised, two-treatment, two-sequence, two-period, two-way crossover, single dose of each formulation (test and reference), bioequivalence study

**Objective**

The objectives of this study were to compare the relative bioavailability of Alendronate sodium 70 mg tablets (manufactured by Dr. Reddy’s Laboratories Limited) with that of ‘FOSAMAX®’ (alendronate sodium) 70 mg tablets (manufactured by Merck Sharp and Dohme limited, UK) in healthy, adult, human subjects under fasting conditions and to monitor safety of the subjects.

**Test and reference products**

Test product: Alendronate sodium 70mg tablets Dr. Reddy’s Lab Ltd
Reference product: Fosamax 70mg tablets Merck UK (#R6601); one tablet each; Oral.

The batch size of the product used in the studies was 150,000 tablets and thus fulfils the batch size requirements for bioequivalence studies.

**Assessor's comment:** The batch size of the test tablet is adequate. The reference product is considered acceptable.
A single oral dose of Alendronate sodium 70 mg was administered in each period of the study with 240 ml of drinking water after an overnight fast of at least 10 hours. The subjects received the test product in one study period and the reference product in the other period. The order of administration was according to the randomization schedule. There was a 21-day interval between treatments.

This study design is based on the assessment of Alendronate in plasma.

Subjects were confined at the clinical facility from at least 11 hours prior to dosing until after the 24 hours post dose. The interval between doses was 21 days.

Blood samples were collected pre-dose and at intervals over 48 hours after each dose.

The plasma samples from the subjects were assayed for alendronate.

**Assessor's comment**
The study design agrees with national and EMEA guidelines on bioavailability/bioequivalence studies. The interval between the periods of 21 days is sufficiently long. The number of subjects in the study is adequate and the conduct of the study, as described in the report is consistent with the principle of GCP.

**Analytical methods**
The analysis to determine the plasma concentrations of alendronate in the study samples was performed using an API 4000 LC/MS/MS system.

**Table 1. Pharmacokinetic parameters of alendronate after oral administration of a 70 mg capsule for the 4 subjects**

<table>
<thead>
<tr>
<th>PK Parameters</th>
<th>Alendronate (Mean ± SD, n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0–7 h (ng/ml/h)</td>
<td>118.55 ± 27.55</td>
</tr>
<tr>
<td>AUCinf (ng/ml/h)</td>
<td>129.37 ± 25.67</td>
</tr>
<tr>
<td>Cmax (ng/ml)</td>
<td>40.94 ± 19.60</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>1.00 ± 0.41</td>
</tr>
<tr>
<td>CL (L/h)</td>
<td>0.56 ± 0.11</td>
</tr>
<tr>
<td>Vd (L)</td>
<td>1.38 ± 0.65</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>1.67 ± 0.50</td>
</tr>
</tbody>
</table>

Over 7 hours, the 70 mg dose the reported plasma concentration was about 10 ng/ml.

**Assessor's comment:**
The analytical method is acceptable and sufficiently validated. The study has been conducted according to GLP, and stability of the samples has been sufficiently demonstrated.

**Pharmacokinetic Variables**
The parameters monitored during the study included $C_{\text{max}}$, $\text{AUC}_{0-1}$, and $\text{AUC}_{0-\infty}$. Pharmacokinetic parameters derived from these measurements of concentration have been log transformed prior to statistical analysis indicators of bioequivalence for solid oral dosage forms. The protocol defined parametric measures for these parameters are:
C<sub>max</sub>: 75% – 133%
AUC<sub>0-t</sub> and AUC<sub>0-∞</sub>: 80% – 125%

**Assessor's comment:** The pharmacokinetic variables are adequate for assessing bioequivalence for Alendronate plasma data.

**Safety:**
Adverse events, standard laboratory evaluation were reported. Descriptive only (adverse events; alterations in the analytical examination of safety; alterations in vital constants; ECG alterations)

**Statistical methods**
The analytical data was used to calculate the pharmacokinetic parameters: AUC<sub>0-t</sub>, AUC<sub>0-∞</sub>, C<sub>max</sub>, T<sub>max</sub>, K<sub>e</sub>, and T<sub>1/2</sub>. The pharmacokinetic parameters and drug plasma concentrations were evaluated statistically for differences due to treatments, period, dosing sequence and subjects within sequence.

**Results**

**Table 2: Log transformed (geometric means) PK parameters:**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Dr Reddy’s 70mg tablets (B#EC7295)</th>
<th>UK reference Fosamax 70mg tablets (B#R6601)</th>
<th>T/R ratios</th>
<th>90% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>63.906</td>
<td>63.984</td>
<td>98.5%</td>
<td>88.6;109</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt; (ng.h/mL)</td>
<td>188.971</td>
<td>184.730</td>
<td>102%</td>
<td>92.1;109</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-∞&lt;/sub&gt; (ng.h/mL)</td>
<td>198.624</td>
<td>196.838</td>
<td>101%</td>
<td>88.6;109</td>
</tr>
</tbody>
</table>

**Table 3: Untransformed (Arithmetic Means) PK parameters:**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Dr Reddy’s 70mg tablets (B#EC7295)</th>
<th>UK reference Fosamax 70mg tablets (B#R6601)</th>
<th>T/R ratios</th>
<th>90% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>72.55220</td>
<td>75.31650</td>
<td>98.5%</td>
<td>89.7;115</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt; (ng.h/mL)</td>
<td>220.9987</td>
<td>215.7383</td>
<td>102%</td>
<td>92.1;109</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-∞&lt;/sub&gt; (ng.h/mL)</td>
<td>231.8336</td>
<td>229.8076</td>
<td>101%</td>
<td>87.9; 114</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt;</td>
<td>1.086129</td>
<td>1.078768</td>
<td>101%</td>
<td>92.8; 109</td>
</tr>
</tbody>
</table>

The data indicates that the conditions of bioequivalence are met and the pharmacokinetic parameters fall within the required 80% - 125% (0.8 – 1.25) range. Thus bioequivalence is demonstrated to the European reference product.

AUC<sub>0-t</sub> area under the plasma concentration-time curve from time zero to t hours
AUC<sub>0-∞</sub> area under the plasma concentration-time curve from time zero to infinity
C<sub>max</sub> maximum plasma concentration
C<sub>min</sub> minimum plasma concentration
PTF% fluctuation index
Summary of results: For the log-transformed alendronate data, the 90% confidence intervals about the ratio of the Test geometric mean to Reference geometric mean are within the 80% to 125% limits for AUC0-t, AUC0-inf, and Cmax.

Assessor's comment: Although the predefined CI for \( C_{\text{max}} \) was wide (75% - 133%), the results reported were within the CI limit of 80% - 125%.

Safety
There were no serious adverse events reported during the study.

Assessor's overall comments:

- One single dose bioequivalence study was submitted using plasma data was to support the current application.
- The batch size of the test tablet is adequate. The reference product is considered acceptable.
- The study design agrees with national and EMEA guidelines on bioavailability/bioequivalence studies. The interval between the periods of 21 days is sufficiently long.
- The number of subjects in the study is adequate and the conduct of the study, as described in the report is consistent with the principle of GCP.
- The analytical method is acceptable and sufficiently validated. The study has been conducted according to GLP, and stability of the samples has been sufficiently demonstrated.
- The linearity, precision, accuracy, recovery, selectivity, stability and limit of detection were determined.
- The pharmacokinetic variables are adequate for assessing bioequivalence for Alendronate plasma data.
- Although the predefined CI for \( C_{\text{max}} \) was wide (75% - 133%), the results reported were within the CI limit of 80% - 125%.
- Based on the submitted bioequivalence study, the Dr. Reddy’s Laboratories Limited 70 mg tablets and the Merck Sharp and Dohme Limited, UK 70 mg tablets (‘FOSAMAX®’) have been shown to be bioequivalent under fasting conditions.
- There were no serious adverse events reported during the study.

Pharmacokinetic conclusion
Based on the submitted bioequivalence study, the Dr. Reddy’s Laboratories Limited 70 mg tablets and the Merck Sharp and Dohme Limited, UK 70 mg tablets (‘FOSAMAX®’) have been shown to be bioequivalent under fasting conditions.

Pharmacodynamic studies
No new pharmacodynamic or clinical data were submitted for this application and none were required. Regarding safety, no serious or unexpected adverse events were identified in the expert report.

Additional data
None.

Post marketing experience
No post-marketing data is available. The medicinal product has not been marketed in any country.

As for the Periodic Safety Update Report (PSUR) the Applicant has stated that:
“The Applicant would like to propose the harmonisation of PSUR to either the EU Harmonised Birth Date if available or the first date of authorisation within this decentralised procedure. Due to the generic status of the product and referring to Volume 9A, Section 6.2.4.c, Part I “Circumstances
Where the Periodicity May Be Amended”, dated January 2007, we would like to request for an amendment of the PSUR cycle to 3 yearly periods from the beginning. The reasons for this request is the well known status of the substance as being on the market in the Member States since for many years, for the same pharmaceutical form as the reference product. As also stated in the medical expert report, the product has a well-recognised efficacy and level of safety in the same indications which justify an amendment of the PSUR cycle to 3 yearly periods, corresponding to the originator’s PSUR cycle.

The RMS accepts this.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Alendronic acid 70mg Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for an application of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Alendronic acid 70mg Tablets and Fosamax 70mg Tablets, PL 00025/0399 (Merck, Sharp and Dohme Ltd, UK). No new or unexpected safety concerns arise from this application.

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

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s product and the innovator product are interchangeable. Extensive clinical experience with alendronic acid is considered to have demonstrated the therapeutic value of the compound. The benefit risk is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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