Public Assessment Report

Decentralised Procedure

Alendronic Acid 70mg Tablets

UK/H/1032/001/DC
UK licence no: PL 18866/0054

Rockspring Healthcare Limited
LAY SUMMARY

On 31st October 2007, the MHRA granted Rockspring Healthcare Limited a Marketing Authorisation (licence) for the medicinal product Alendronic Acid 70mg Tablets (PL 18866/0054). These are prescription only medicines (POM) for the treatment of postmenopausal osteoporosis.

The active ingredient, alendronate monosodium trihydrate, belongs to a group of medicines called bisphosphonates. It works by preventing the loss of bone that occurs in women after they have been through the menopause, and helps to rebuild bone.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Alendronic Acid 70mg Tablets outweigh the risks; hence a Marketing Authorisation has been granted.
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# Module 1

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Alendronic Acid 70mg Tablets</th>
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<tbody>
<tr>
<td>Type of Application</td>
<td>Article 10.1, Generic Application</td>
</tr>
<tr>
<td>Active Substance</td>
<td>Alendronate sodium trihydrate</td>
</tr>
<tr>
<td>Form</td>
<td>Tablets</td>
</tr>
<tr>
<td>Strength</td>
<td>70mg</td>
</tr>
<tr>
<td>MA Holder</td>
<td>Rockspring Healthcare Limited, 38/40 Chamberlayne Road, London, NW10 3JE</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Concerned Member States</td>
<td>Czech Republic, Germany, Italy, The Netherlands, Poland and Slovakia</td>
</tr>
<tr>
<td>Procedure Number</td>
<td>UK/H/1032/0001/DC</td>
</tr>
<tr>
<td>Timetable</td>
<td>Day 120 – 9th October 2007</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 the equivalent of 70 mg of alendronic acid as 91.37 mg alendronate monosodium trihydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet.

White oval flat tablets, with dimensions of 14 x 8 mm and marked on one face with “70”

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Treatment of postmenopausal osteoporosis. Sodium alendronate 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 alendronate:

Sodium alendronate must be taken at least 30 minutes before the first food, beverage, or medicinal product of the day with plain water only. Other beverages (including mineral water), food and some medicinal products are likely to reduce the absorption of alendronate (see 4.5 'Interaction with other medicinal products and other forms of interaction').

To facilitate delivery to the stomach and thus reduce the potential for local and oesophageal irritation/adverse experiences (see 4.4 'Special warnings and precautions for use'):
• Sodium alendronate should only be swallowed upon arising for the day with a full glass of water (not less than 200 ml or 7 fl.oz.).
• Patients should not chew the tablet or allow the tablet to dissolve in their mouths because of a potential for oropharyngeal ulceration.
• Patients should not lie down until after their first food of the day which should be at least 30 minutes after taking the tablet.
• Patients should not lie down for at least 30 minutes after taking Sodium alendronate.
• Sodium alendronate should not be taken at bedtime or before arising for the day.

Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate (see 4.4 'Special warnings and precautions for use').

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

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

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

Sodium alendronate 70 mg Tablets has not been investigated in the treatment of glucocorticoid-induced osteoporosis.
4.3 **Contraindications**
- Hypersensitivity to sodium alendronate or any to the excipients
- 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.
- Hypocalcaemia.
- See also 4.4 'Special warnings and precautions for use'.

4.4 **Special warnings and precautions for use**
Alendronate can cause local irritation of the upper gastro-intestinal mucosa. Because there is a potential for worsening of the underlying disease, caution should be used when alendronate is given to patients with active upper gastro-intestinal problems, such as dysphagia, oesophageal disease, gastritis, duodenitis, ulcers, or with a recent history (within the previous year) of major gastro-intestinal disease such as peptic ulcer, or active gastro-intestinal bleeding, or surgery of the upper gastro-intestinal tract other than pyloroplasty (see 4.3 'Contra-indications').

Oesophageal reactions (sometimes severe and requiring hospitalisation), such as oesophagitis, oesophageal ulcers and oesophageal erosions, rarely followed by oesophageal stricture, have been reported in patients receiving alendronate. Physicians should therefore be alert to any signs or symptoms signaling a possible oesophageal reaction and patients should be instructed to discontinue alendronate and seek medical attention if they develop symptoms of oesophageal irritation such as dysphagia, pain on swallowing or retrosternal pain, new or worsening heartburn.

The risk of severe oesophageal adverse experiences appears to be greater in patients who fail to take alendronate properly and/or who continue to take alendronate after developing symptoms suggestive of oesophageal irritation. It is very important that the full dosing instructions are provided to, and understood by the patient (see 4.2 'Posology and method of administration'). Patients should be informed that failure to follow these instructions may increase their risk of oesophageal problems.

While no increased risk was observed in extensive clinical trials, there have been rare (post-marketing) reports of gastric and duodenal ulcers, some severe and with complications. A causal relationship cannot be ruled out.

Patients should be instructed that if they miss a dose of Sodium alendronate 70 mg, they should take one tablet on the morning after they remember. They should not take two tablets on the same day but should return to taking one tablet once a week, as originally scheduled on their chosen day.

Alendronate is not recommended for patients with renal impairment where GFR is less than 35 ml/min, (see 4.2 'Posology and method of administration').

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

Hypocalcaemia must be corrected before initiating therapy with alendronate (see 4.3 'Contra-indications'). 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 Sodium alendronate.

Due to positive effects of alendronate in increasing bone mineral, decreases in serum calcium and phosphate may occur. These are usually small and asymptomatic. However, there have been reports of symptomatic hypocalcaemia, which occasionally have been severe and often occurred in patients with predisposing conditions (e.g. hypoparathyroidism, vitamin D deficiency and calcium malabsorption). Ensuring adequate calcium and vitamin D intake is therefore particularly important in patients receiving glucocorticoids.

4.5 **Interaction with other medicinal products and other forms of interaction**
If taken at the same time, it is likely that food and beverages (including mineral water), calcium supplements, antacids, and some oral medicinal products will interfere with absorption of alendronate. Therefore, patients must wait at least 30 minutes after taking alendronate before taking any other oral medicinal product (see 4.2 'Posology and method of administration' and 5.2 'Pharmacokinetic properties').
No other interactions with medicinal products of clinical significance are anticipated. A number of patients in the clinical trials received oestrogen (intravaginal, transdermal, or oral) while taking alendronate. No adverse experiences attributable to their concomitant use were identified.

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

4.6 Pregnancy and lactation
There are no adequate data from the use of alendronate monosodium trihydrate in pregnant women. Animal studies do not indicate direct harmful effects with respect to pregnancy, embryonal/foetal development, or postnatal development. Alendronate given during pregnancy in rats caused dystocia related to hypocalcemia (see 5.3 'Preclinical safety data'). Given the indication, alendronate should not be used during pregnancy.

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

4.7 Effects on ability to drive and use machines
Sodium Alendronate has no influence 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 'Fosamax' Once Weekly 70 mg (n = 519) and alendronate 10 mg/day (n = 370) were similar.

In two three-year studies of virtually identical design, in post-menopausal women (alendronate 10 mg: n = 196, placebo: n = 397) the overall safety profiles of alendronate 10 mg/day and placebo were similar.

Adverse experiences reported by the investigators as possibly, probably or definitely drug-related are presented below if they occurred in ≥1% in either treatment group in the one-year study, or in ≥1% of patients treated with alendronate 10 mg/day and at a greater incidence than in patients given placebo in the three-year studies:

<table>
<thead>
<tr>
<th></th>
<th>One-Year Study</th>
<th>Three-Year Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>'Fosamax' Once Weekly 70 mg (n = 519)</td>
<td>Alendronate 10 mg/day (n = 370)</td>
</tr>
<tr>
<td>Gastro-intestinal</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>Musculoskeletal</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>Neurological</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)**
*Gastro-intestinal:* abdominal pain, dyspepsia, constipation, diarrhoea, flatulence, oesophageal ulcer*, dysphagia*, abdominal distension, acid regurgitation.
*Musculoskeletal:* musculoskeletal (bone, muscle or joint) pain.
*Neurological:* headache.

**Uncommon (≥1/1,000, <1/100)**
*Body as a whole:* rash, pruritus, erythema
*Gastro-intestinal:* nausea, vomiting, gastritis, oesophagitis*, oesophageal erosions*, melaena.

**Rare (≥1/10,000, <1/1,000)**
*Body as a whole:* hypersensitivity reactions including urticaria and angioedema. Transient symptoms as in an acute-phase response (myalgia, malaise and rarely, fever), typically in association with initiation of treatment. Rash with photosensitivity. Symptomatic hypocalcaemia, often in association with predisposing conditions (see 4.4 'Special warnings and precautions for use').
*Gastro-intestinal:* oesophageal stricture*, oropharyngeal ulceration*, upper gastrointestinal PUBs (perforation, ulcers, bleeding), although a causal relationship cannot be ruled out.
*Special senses:* uveitis, scleritis, episcleritis.

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

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

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

4.9 Overdose
Hypocalcaemia, hypophosphataemia and upper gastro-intestinal adverse events, such as upset stomach, heartburn, oesophagitis, gastritis, or ulcer, may result from oral overdosage.

No specific information is available on the treatment of overdosage with alendronate. Milk or antacids should be given to bind alendronate. Owing to the risk of oesophageal irritation, vomiting should not be induced and the patient should remain fully upright.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
*Pharmacotherapeutic group:* Bisphosphonate, for the treatment of bone diseases.
ATC Code: M05B A04

The active ingredient of Sodium alendronate 70 mg Tablets, alendronate monosodium trihydrate, is a bisphosphonate that inhibits osteoclastic bone resorption with no direct effect on bone formation. Preclinical studies have shown preferential localisation of alendronate to sites of active resorption. Activity of osteoclasts is inhibited, but recruitment or attachment of osteoclasts is not affected. The bone formed during treatment with alendronate is of normal quality.

*Treatment of post-menopausal osteoporosis*
Osteoporosis is defined as BMD of the spine or hip 2.5 SD below the mean value of a normal young population or as a previous fragility fracture, irrespective of BMD.

The therapeutic equivalence of 'Fosamax' Once Weekly 70 mg (n=519) and alendronate 10 mg daily (n=370) was demonstrated in a one-year multicentre study of post-menopausal women with osteoporosis. The mean increases from baseline in lumbar spine BMD at one year were 5.1% (95% CI: 4.8, 5.4%) in the 70 mg once-weekly group and 5.4% (95% CI: 5.0, 5.8%) in the 10 mg daily group. The mean BMD increases were 2.3% and 2.9% at the femoral neck and 2.9% and 3.1% at the total hip.
in the 70 mg once weekly and 10 mg daily groups, respectively. The two treatment groups were also similar with regard to BMD increases at other skeletal sites.

The effects of alendronate on bone mass and fracture incidence in post-menopausal women were examined in two initial efficacy studies of identical design (n=994) as well as in the Fracture Intervention Trial (FIT: n=6,459).

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

FIT consisted of two placebo-controlled studies using alendronate daily (5 mg daily for two years and 10 mg daily for either one or two additional years):

• FIT 1: A three-year study of 2,027 patients who had at least one baseline vertebral (compression) fracture. In this study alendronate daily reduced the incidence of 1 new vertebral fracture by 47% (alendronate 7.9% vs placebo 15.0%). In addition, a statistically significant reduction was found in the incidence of hip fractures (1.1% vs. 2.2%, a reduction of 51%).

• FIT 2: A four-year study of 4,432 patients with low bone mass but without a baseline vertebral fracture. In this study, a significant difference was observed in the analysis of the subgroup of osteoporotic women (37% of the global population who correspond with the above definition of osteoporosis) in the incidence of hip fractures (alendronate 1.0% vs. placebo 2.2%, a reduction of 56%) and in the incidence of 1 vertebral fracture (2.9% vs. 5.8%, a reduction of 50%).

5.2 Pharmacokinetic properties

Absorption
Relative to an intravenous reference dose, the oral mean bioavailability of alendronate in women was 0.64% for doses ranging from 5 to 70 mg when administered after an overnight fast and two hours before a standardised breakfast. Bioavailability was decreased similarly to an estimated 0.46% and 0.39% when alendronate was administered one hour or half an hour before a standardised breakfast. In osteoporosis studies, alendronate was effective when administered at least 30 minutes before the first food or beverage of the day.

Bioavailability was negligible whether alendronate was administered with, or up to two hours after, a standardised breakfast. Concomitant administration of alendronate with coffee or orange juice reduced bioavailability by approximately 60%.

In healthy subjects, oral prednisone (20 mg three times daily for five days) did not produce a clinically meaningful change in oral bioavailability of alendronate (a mean increase ranging from 20% to 44%).

Distribution
Studies in rats show that alendronate transiently distributes to soft tissues following 1 mg/kg intravenous administration but is then rapidly redistributed to bone or excreted in the urine. The mean steady-state volume of distribution, exclusive of bone, is at least 28 litres in humans. Concentrations of drug in plasma following therapeutic oral doses are too low for analytical detection (<5 ng/ml). Protein binding in human plasma is approximately 78%.

Biotransformation
There is no evidence that alendronate is metabolised in animals or humans.

Elimination
Following a single intravenous dose of [14C]alendronate, approximately 50% of the radioactivity was excreted in the urine within 72 hours and little or no radioactivity was recovered in the faeces. Following a single 10 mg intravenous dose, the renal clearance of alendronate was 71 ml/min, and systemic clearance did not exceed 200 ml/min. Plasma concentrations fell by more than 95% within six hours following intravenous administration. The terminal half-life in humans is estimated to exceed ten years, reflecting release of alendronate from the skeleton. Alendronate is not excreted through the
acidic or basic transport systems of the kidney in rats, and thus it is not anticipated to interfere with the excretion of other medicinal products by those systems in humans.

Characteristics in patients
Preclinical studies show that the drug that is not deposited in bone is rapidly excreted in the urine. No evidence of saturation of bone uptake was found after chronic dosing with cumulative intravenous doses up to 35 mg/kg in animals. Although no clinical information is available, it is likely that, as in animals, elimination of alendronate via the kidney will be reduced in patients with impaired renal function. Therefore, somewhat greater accumulation of alendronate in bone might be expected in patients with impaired renal function (see 4.2 'Posology and method of administration').

5.3 Preclinical safety data
Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. Studies in rats have shown that treatment with alendronate during pregnancy was associated with dystocia in dams during parturition which was related to hypocalcaemia. In studies, rats given high doses showed an increased incidence of incomplete foetal ossification. The relevance to humans is unknown.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Microcrystalline cellulose
Crospovidone
Magnesium stearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 months

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
Al/Al blister
Packs of 2, 4, 8, 12, & 40 tablets.

Not all pack sizes may be marketed

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Rockspring Healthcare Limited
38/40 Chamberlayne Road,
London, NW10 3JE
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 18866/0054

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
31/10/2007

10 DATE OF REVISION OF THE TEXT
31/10/2007

11 DOSIMETRY (IF APPLICABLE)

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)
Module 3

PACKAGE LEAFLET
ALENDRONIC ACID 70 MG TABLETS

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you personally and you should 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 become 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 70 mg Tablets are and what they are used for
2. Before you take Alendronic Acid 70 mg Tablets
3. How to take Alendronic Acid 70 mg Tablets
4. Possible side effects
5. How to store Alendronic Acid 70 mg Tablets
6. Further Information

1. WHAT ALENDRONIC ACID 70 MG TABLETS ARE AND WHAT THEY ARE USED FOR
The active ingredient, alendronate monosodium trihydrate, belongs to a group of medicines called "bisphosphonates". It works by preventing the loss of bone that occurs in women after they have been through the menopause, and helps to rebuild bone.
Alendronic Acid is used to treat the following condition:
- Postmenopausal osteoporosis.

2. BEFORE YOU TAKE ALENDRONIC ACID 70 MG TABLETS
If any of the following applies to you, speak to your doctor or pharmacist before you start taking Alendronic Acid 70 mg Tablets as they may not be suitable for you.
Do not take Alendronic Acid 70 mg Tablets:
- if you are allergic (hypersensitive) to alendronate monosodium trihydrate or any of the other ingredients of Alendronic Acid 70 mg Tablets.
- if you have certain disorders of the oesophagus (the tube that connects your mouth with your stomach).
- if you are unable to stand or sit upright for at least 30 minutes.
- if your doctor has told you that you have low blood calcium.
- if you are or think you may be pregnant.
- if you are breast-feeding.
Take special care with Alendronic Acid 70 mg Tablets:
It is important to talk to your doctor if you have any of the following conditions:
- you suffer from kidney problems
- you have any allergies
- you have trouble swallowing or digestive problems.

Taking other medicines:
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without prescription.
- After swallowing your tablet, wait at least 30 minutes before taking any other medication for the day. Alendronic Acid 70 mg Tablets are only effective if taken when your stomach is empty.

Taking Alendronic Acid 70 mg Tablets with food and drink:
Patients must wait at least 30 minutes after taking alendronate before taking any food or drink.

Pregnancy and breast-feeding:
Alendronic Acid 70 mg Tablets can be used during pregnancy and if you are breast-feeding.

Driving and using machines:
Your medicine does not usually affect your ability to drive or operate machinery.

Other precautions you should take:
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE ALENDRONIC ACID 70 MG TABLETS
Your doctor has decided on the dose that is suited to you. The length of your course of treatment will depend on what condition you are suffering from.
Always take Alendronic Acid 70 mg Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
You may have previously been prescribed a 10 mg tablet of alendronate which is taken once a day. One Alendronic Acid 70 mg Tablet is taken once a week.
It is very important that you follow actions 2, 3, 4 and 6 described below. This will help the Alendronic Acid 70 mg Tablet reach your stomach quickly and help reduce the risk of irritating your oesophagus.

1. Choose the day of the week that best fits your schedule. Every week, take your Alendronic Acid 70 mg Tablet on your chosen day.
2. After getting up for the day and before taking your first food, drink or other medication, swallow your Alendronic Acid 70 mg Tablet with a full glass of plain water only (not less than 200 ml or 7 fl oz.).
Do not chew or allow the tablet to dissolve in your mouth.
3. After swallowing your Alendronic Acid 70 mg Tablet do not lie down — stay fully upright (or sat upright) for at least 30 minutes and do not lie down until after your first food of the day.
4. Do not take Alendronic Acid 70 mg Tablets at bedtime or before getting up for the day.
5. If you develop difficulty or pain swallowing, chest pain, or new or worsening heartburn, stop taking Alendronic Acid 70 mg Tablets and contact your doctor.
6. After swallowing your Alendronic Acid 70 mg Tablet, wait at least 30 minutes before taking your first food, drink or other medication of the day, including antacids, calcium supplements and vitamins. Alendronic Acid 70 mg Tablets are only effective if taken when your stomach is empty.

If you take more Alendronic Acid 70 mg Tablets than you should:
If you (or someone else) accidentally take too many Alendronic Acid 70 mg Tablets, drink a full glass of milk and contact your doctor or pharmacist immediately.
If you forget to take Alendronic Acid 70 mg Tablets:
If you forget to take a dose, take one Alendronic Acid 70 mg Tablet on the morning after you remember. Do not take a double dose to make up for forgotten individual doses.

If you stop taking Alendronic Acid 70 mg Tablets:
Always contact your doctor or pharmacist before you stop taking Alendronic Acid 70 mg Tablets. Alendronic Acid 70 mg 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 70 mg tablets can cause side effects, although not everybody gets them. These are usually mild but some patients may experience digestive disturbances which may be severe.

If the following happens, stop taking the tablets and tell your doctor immediately or go to the accident and emergency department at your nearest hospital:
- An allergic reaction (angioedema): swelling of the face, lips, tongue or throat, or difficulty breathing or swallowing.

This is a very serious but rare side effect. You may need urgent medical attention or hospitalisation.

Side effects sometimes seen are:
- Common – more than one in a hundred people but less than one in ten:
  - Gastro-intestinal: stomach pain, constipation, diarrhea, flatulence, oesophageal ulcer, acid regurgitation, swollen abdomen, swallowing difficulties, digestive problems.
  - Musculoskeletal: bone, muscle or joint pain.

- Uncommon – more than one in a thousand people but less than one in a hundred:
  - Body as a whole: rash, reddening of the skin, itching.

- Rare – more than one in ten thousand people but less than one in a thousand:
  - Body as a whole: allergic reaction including hives and swelling of the lips, tongue and throat, fever, discomfort, muscle pains, rash (occasionally made worse by sunlight), reduced blood calcium levels.
  - Gastro-intestinal: difficulty in swallowing, ulcers of the mouth, stomach and other peptic ulcers (some with bleeding).

Special senses: eye pain, diminished or hazy vision and/or seeing black floating spots.

If any of the side effects become 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 70 MG TABLETS

Keep out of the reach and sight of children.
This medicinal product does not require any special storage conditions.
Do not use Alendronic Acid 70 mg Tablets after the expiry date which is stated on the outer packaging.
The expiry date refers to the last day of the month.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Alendronic Acid 70 mg Tablets contain:
- The active substance is alendronate monosodium trihydrate and each tablet contains 70 mg of alendronate monosodium trihydrate.
- The other ingredients are microcrystalline cellulose, crospovidone and magnesium stearate.

What Alendronic Acid 70 mg Tablets look like and contents of the pack
Each tablet is white, oval, flat and marked with a "70" on one side.
Alendronic Acid 70 mg Tablets are available in blisters of 2, 4, 8, 12, 40 tablets.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder: Rockspring Healthcare Limited, 38/40 Chamberlayne Road, London, NW10 3DE. P.L. 10060/0054

This leaflet was last updated in June 2006

ROCKSPRING HEALTHCARE LTD.
Module 4
Labelling

Alendronic Acid 70 mg Tablets
(Alendronate monosodium trihydrate)

Batch No

ROCKSPRING HEALTHCARE LTD.

MA Holder: Rockspring Healthcare Limited,
London, NW10 3JE.
Alendronic Acid 70 mg Tablets
(Alendronate monosodium trihydrate)
2 Tablets
Each tablet contains alendronate monosodium trihydrate equivalent to 70 mg alendronic acid.

For oral administration.
Use only as directed by your physician.
Keep out of the reach and sight of children.
Read the package leaflet before use.
This medicinal product does not require any special storage conditions.

POM
PL 18866/0054
Alendronic Acid 70 mg Tablets
(Alendronate monosodium trihydrate)
4 Tablets

Each tablet contains alendronate monosodium trihydrate equivalent to 70 mg alendronic acid.

MA Holder: Rockspring Healthcare Limited,
36,40 Chamblyste Road, London, NW10 3JE, United Kingdom.

For oral administration.
Use only as directed by your physician.
Keep out of the reach and sight of children.
Read the package leaflet before use.
This medicinal product does not require any special storage conditions.
Alendronic Acid 70 mg Tablets
(Alendronate monosodium trihydrate)

Each tablet contains alendronate monosodium trihydrate equivalent to 70 mg alendronic acid.

For oral administration.
Use only as directed by your physician.
Keep out of the reach and sight of children.
Read the package leaflet before use.
This medicinal product does not require any special storage conditions.

POM

PL 18866/0084
Module 5

Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the UK granted a marketing authorisation for the medicinal product Alendronic Acid 70mg Tablets (PL 18866/0054) on 31st October 2007. The products are prescription-only medicines.

These are applications made under Article 10.1 of 2001/83 EC, as amended, for a generic medicinal product to Fosamax 70mg Tablets (Merck, Sharp and Dohme Ltd, UK), which was granted a licence in at least one European Union state at least 10 years ago.

The product contains the active ingredient alendronate monosodium trihydrate and is indicated for the treatment of postmenopausal osteoporosis. Sodium alendronate reduces the risk of vertebral and hip fractures.

Alendronate monosodium trihydrate is a bisphosphonate that acts as a potent inhibitor of osteoclast-mediated bone resorption.

No new preclinical studies were conducted, which is acceptable given that the application was based on a generic medicinal product to a product that has been licensed for over 10 years.

No clinical studies were conducted, which is acceptable given that the application is for a generic medicinal product to a product that has been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

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. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites.

The decentralised procedure was completed at Day 120 (9th October 2007), with the reference member state and all concerned member states agreeing that the licence was approvable. The national phase of the decentralised procedure was completed in the UK on 31st October 2007.
II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Alendronic Acid 70mg Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Alendronate monosodium trihydrate</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Bisphosphonate (M05B A04)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>70mg Tablets</td>
</tr>
<tr>
<td>Reference numbers for the Decentralised Procedure</td>
<td>UK/H/1032/001/DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Member States concerned</td>
<td>Czech Republic, Germany, Italy, The Netherlands, Poland and Slovakia</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 18866/0054</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Rockspring Healthcare Limited</td>
</tr>
<tr>
<td></td>
<td>38/40 Chamberlayne Road, London, NW10 3JE</td>
</tr>
<tr>
<td></td>
<td>United Kingdom</td>
</tr>
</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

INN: Alendronate monosodium trihydrate

Chemical Name: (4-amino-1-hydroxybutylidene)bisphosphonic acid mono sodium salt

CAS Registry No: 121268-17-5

Molecular Formula: C₄H₁₂NNaO₇P₂

Structure:

```
\[
\begin{array}{c}
\text{C}_4\text{H}_{12}\text{NNaO}_7\text{P}_2 \\
\end{array}
\]
```

Molecular Weight: 325.12

Appearance: White or almost white crystalline powder

Solubility: Soluble in water

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

All potential known impurities have been identified and characterised. Appropriate proof of structure data has been supplied for the active pharmaceutical ingredient.

An appropriate specification is provided for the active substance alendronate monosodium trihydrate. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

The active substance is packaged in double polyethylene bags, closed with plastic cords and sealed in drums. Specifications for all packaging used have been provided and are satisfactory. A declaration has been provided that the primary packaging complies with current regulations concerning contact with foodstuff.

Appropriate stability data have been provided to support a retest period of 3 years when stored in the proposed packaging.

P Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipients crospovidone, cellulose microcrystalline and magnesium stearate.
All excipients used comply with respective European Pharmacopoiea monographs. Satisfactory certificates of analysis have been provided for all excipients.

None of the excipients used contain materials of animal or human origin.

**Pharmaceutical Development**
The applicant has provided a suitable product development rationale and data. Comparable dissolution and impurity profiles have been provided for batches of the proposed product versus reference product.

**Manufacture**
Satisfactory batch formulae have been provided for the manufacture of the product along with an appropriate account of the manufacturing process. Suitable in-process controls are applied during the manufacturing process to ensure the quality of the product.

The manufacturing process has been validated and has shown satisfactory results.

**Control of Drug Product**
The finished product specification proposed is acceptable and provides an assurance of the quality of the finished product. The analytical methods used have been suitably validated. Batch analysis data have demonstrated compliance with the proposed specification.

Satisfactory data on the characterisation of impurities have been provided.

**Reference Standards or Materials**
Certificates of analysis for all reference standards used have been provided and are satisfactory.

**Container Closure System**
The finished product is packaged in aluminium/aluminium – PA - PVC blisters in pack sizes of 2, 4, 8, 12 and 40 tablets.

**Stability of the Drug Product**
Stability data provided to support a shelf-life of 36 months, with no specific storage conditions.

**Bioequivalence/Bioavailability**
Certificates of analysis have been provided for batches of test and reference product used in the bioequivalence study.

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

The PIL is in compliance with current guidelines and user testing results have been submitted. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

**CONCLUSION**
It is recommended that marketing authorisations are granted for these applications.
III.2 PRE-CLINICAL ASPECTS
Specific non-clinical studies have not been performed, which is acceptable for this generic abridged application. The non-clinical overview provides a reasonable update on the known pharmacological and toxicological properties of alendronate monosodium trihydrate.

III.3 CLINICAL ASPECTS

PHARMACODYNAMICS
No new pharmacodynamic data have been provided and none are required for an application of this type.

PHARMACOKINETICS
With the exception of the bioequivalence study, no new pharmacokinetic data have been provided and none are required for an application of this type.

EFFICACY
No new efficacy data have been provided and none are required for an application of this type.

A single-dose, randomised, open-label, crossover, two-period study was conducted comparing the urinary pharmacokinetics of the proposed product (Alendronic Acid 70mg Tablets) versus the reference product (Fosamax 70mg Tablets) in healthy volunteers in a fasted state. Urine samples were collected at pre-dose and up to 48 hours post dose, with at least a 14 day washout period between doses.

The results for the main pharmacokinetic parameters are presented below:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Difference</th>
<th>Difference SE</th>
<th>Ratio (%Ref)</th>
<th>CI- 90 Lower</th>
<th>CI- 90 Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \ln (\text{excreted quantity}) )</td>
<td>0.0346</td>
<td>0.0957</td>
<td>103.5</td>
<td>88.3</td>
<td>121.4</td>
</tr>
<tr>
<td>( \ln (\text{Rate}_{\text{max}}) )</td>
<td>0.0435</td>
<td>0.0871</td>
<td>104.5</td>
<td>90.4</td>
<td>120.8</td>
</tr>
<tr>
<td>( \ln (\text{AUC}_{\text{last}}) )</td>
<td>0.0252</td>
<td>0.0945</td>
<td>102.6</td>
<td>87.6</td>
<td>120.0</td>
</tr>
<tr>
<td>( \ln (\text{AUC}_{\text{inf}}) )</td>
<td>0.0255</td>
<td>0.0937</td>
<td>102.6</td>
<td>87.8</td>
<td>119.9</td>
</tr>
</tbody>
</table>

*ln-transformed values

The comparative analysis of the kinetic parameters for both formulations was within the bioequivalence intervals. Thus, bioequivalence has been demonstrated between the test and reference products.

SAFETY
No new safety issues have been identified.

EXPERT REPORT
A satisfactory clinical expert report has been submitted, which has been written by an appropriately qualified medical practitioner.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)
This is satisfactory and consistent with the SPC for the reference product.

PATIENT INFORMATION LEAFLET (PIL)
This is satisfactory and consistent with the SPC.

LABELLING
These are satisfactory.
CONCLUSION
There are no clinical objections to the grant of marketing authorisation for this application. Bioequivalence has been successfully shown between this product and the reference product.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and packaging are satisfactory and consistent with those for the reference product.

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 the originator products Fosamax 70mg Tablets (Merck, Sharp and Dohme Ltd, UK).

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with those for the other strengths of this product that have previously been granted licences.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with alendronate monosodium trihydrate is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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