Public Assessment Report

Alendronic Acid 70mg Tablets

Alendronic Sodium Monohydrate

UK/H/833/01

TEVA UK Ltd
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Module</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Module 1: Information about initial procedure</td>
<td>3</td>
</tr>
<tr>
<td>Module 2: Summary of Product Characteristics</td>
<td>4</td>
</tr>
<tr>
<td>Module 3: Product Information Leaflets</td>
<td>10</td>
</tr>
<tr>
<td>Module 4: Labelling</td>
<td>13</td>
</tr>
<tr>
<td>Module 5: Scientific Discussion</td>
<td>16</td>
</tr>
</tbody>
</table>

1 Introduction  
2 Quality aspects  
3 Non-clinical aspects  
4 Clinical aspects  
5 Overall conclusions
**Module 1**

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Alendronic Acid</th>
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</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Abridged</td>
</tr>
<tr>
<td></td>
<td>Initial application</td>
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<tr>
<td></td>
<td>Generic, Article 10.1(a)(iii), first paragraph</td>
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<td></td>
<td>Chemical</td>
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<td>Prescription only</td>
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<tr>
<td><strong>Active Substance</strong></td>
<td>Alendronate Sodium Monohydrate</td>
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<tr>
<td><strong>Form</strong></td>
<td>Tablets</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>70mg</td>
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<tr>
<td><strong>MA Holder</strong></td>
<td>TEVA</td>
</tr>
<tr>
<td><strong>RMS</strong></td>
<td>United Kingdom</td>
</tr>
<tr>
<td><strong>CMS</strong></td>
<td>Austria, Belgium, Czech Republic, Germany, Denmark, Spain, France, Hungary, Ireland, Italy, Lithuania, The Netherlands, Norway, Poland, Portugal, Sweden, Slovakia, Estonia, Greece, Latvia, Slovenia.</td>
</tr>
<tr>
<td><strong>Procedure Number</strong></td>
<td>UK/H/833/01</td>
</tr>
<tr>
<td><strong>Timetable</strong></td>
<td>Day 90 December 5th 2005</td>
</tr>
</tbody>
</table>
Module 2

Summary of Product Characteristics

The UK Summary of Product Characteristics (SPC) for Alendronic Acid 70mg Tablets is as follows:

Alendronic Acid (PL 00289/0890)

1. NAME OF THE MEDICINAL PRODUCT
   Alendronic acid 70 mg Tablets

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

3. PHARMACEUTICAL FORM
   Tablet.
   White to off-white, flat-faced bevel-edged round tablet, debossed with T on one side, plain 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.

   For oral use
   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 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 warning and precautions for use'):
   - Alendronic acid should only be swallowed upon arising for the day with a full glass of water (not less than 200 ml or 7 fl. oz.).
   - Patients should not chew the tablet or allow the tablet to dissolve in their mouths because of a potential for oropharyngeal ulceration.
   - Patients should not lie down until after their first food of the day which should be at least 30 minutes after taking the tablet.
   - Patients should not lie down for at least 30 minutes after taking Alendronic acid.
   - 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 4.4 'Special warning and precautions for use').

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

4.3 Contraindications
• Abnormalities of the oesophagus and other factors which delay oesophageal emptying such as stricture or achalasia.
• Inability to stand or sit upright for at least 30 minutes.
• Hypersensitivity to alendronic acid or to any of the excipients.
• Hypocalcaemia.
• See also 4.4 'Special warning and precautions for use'.

4.4 Special Warning 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 4.3 'Contraindications').

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 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 Alendronic acid, they should take one tablet on the morning after they remember. They should not take two tablets on the same day but should return to taking one tablet once a week, as originally scheduled on their chosen day.

Alendronic acid is not recommended for patients with renal impairment where GFR is less than 35 ml/min, (see 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 alendronic acid (see 4.3 'Contraindications'). Other disturbances of mineral metabolism (such as vitamin D deficiency) should also be effectively treated. 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.

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 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 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. Alendronic acid given during pregnancy in rats caused dystocia related to hypocalcaemia (see 5.3 ‘Preclinical safety data’). 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

No effects on ability to drive and use machines have been observed.

4.8 Undesirable Effects

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

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

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

<table>
<thead>
<tr>
<th>Gastrointestinal</th>
<th>One-Year Study</th>
<th>Three-Year Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alendronic acid 70mg (n = 519) %</td>
<td>Alendronic acid 10mg/day (n = 370) %</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>
</tbody>
</table>
The following adverse experiences have also been reported during clinical studies and/or post-marketing use:

**Common (≥1/100, <1/10)**

**Gastrointestinal:** abdominal pain, dyspepsia, constipation, diarrhoea, flatulence, oesophageal ulcer*, melena, 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, erythema

**Gastrointestinal:** nausea, vomiting, gastritis, oesophagitis*, oesophageal erosions*.

**Rare (≥1/10,000, <1/1,000)**

**Body as a whole:** hypersensitivity reactions including urticaria and angioedema. Rash with photosensitivity.

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

**Special senses:** uveitis, scleritis.

* See 4.4 'Special warning 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 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 overdosage.

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

**5 PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic Properties**

**Pharmacotherapeutic group:** Bisphosphonate, for the treatment of bone diseases.

ATC Code: M05B A04

The active ingredient 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 post-menopausal women with osteoporosis. The mean increases from baseline in lumbar spine BMD at one year were 5.1% (95% CI: 4.8, 5.4%) in the 70 mg once-weekly group and 5.4% (95% CI: 5.0, 5.8%) in the 10 mg daily group. The mean BMD increases were 2.3% and 2.9% at the femoral neck and 2.9% and 3.1% at the total hip in the 70 mg once weekly and 10 mg daily groups, respectively. The two treatment groups were also similar with regard to BMD increases at other skeletal sites.
The effects of alendronic acid on bone mass and fracture incidence in post-menopausal women were examined in two initial efficacy studies of identical design (n=994) as well as in the Fracture Intervention Trial (FIT: n=6,459).

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

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

- FIT 1: A three-year study of 2,027 patients who had at least one baseline vertebral (compression) fracture. In this study alendronic acid daily reduced the incidence of new vertebral fracture by 47% (alendronic acid 7.9% vs. placebo 15.0%). In addition, a statistically significant reduction was found in the incidence of hip fractures (1.1% vs. 2.2%, a reduction of 51%).
- FIT 2: A four-year study of 4,432 patients with low bone mass but without a baseline vertebral fracture. In this study, a significant difference was observed in the analysis of the subgroup of osteoporotic women (37% of the global population who correspond with the above definition of osteoporosis) in the incidence of hip fractures (alendronic acid 1.0% vs. placebo 2.2%, a reduction of 56%) and in the incidence of 1 vertebral fracture (2.9% vs. 5.8%, a reduction of 50%).

5.2 Pharmacokinetic Properties

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

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

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

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

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

Elimination
Following a single intravenous dose of [14C]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 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 alendronic acid during pregnancy was associated with dystocia in dams during parturition which was related to hypocalcaemia. Fetuses 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
Croscarmellose sodium
Magnesium stearate

6.2 Incompatibilities
Not applicable

6.3 Shelf Life
30 months

6.4 Special Precautions for Storage
No special storage condition.

6.5 Nature and Contents of Container
Aluminium / aluminium blisters.
Blister packs of 2, 4, 8 (2x4), 12 (3x4), 40 (10x4) & 50 tablets in hospital unit dosage.

6.6 Instructions for Use and Handling
No special requirements

7. MARKETING AUTHORITY
Teva UK Limited
Brampton Road, Hampden Park
Eastbourne, BN22 9AG
United Kingdom

8. MARKETING AUTHORITY NUMBER
PL 00289/0890

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
5th July 2005

10. DATE OF REVISION OF THE TEXT
Module 3

Product Information Leaflet

Leaflet on following pages.
2. BEFORE YOU TAKE ALENDRONIC ACID 70 mg TABLETS

Do not take Alendronic Acid 70 mg Tablets if you:

- Are sensitive to any of the ingredients in this medicine
- Have heart or liver problems
- Have taken too much, or have taken this medicine for more than 1 year
- Have low blood calcium levels

Take special care with Alendronic Acid 70 mg Tablets if you have:

- Difficulty swallowing
- A history of stomach ulcer or peptic ulcer
- A history of poor nutrition or other digestive problems

Other possible side effects you should take:

- Do not take any other medicines at the same time as taking Alendronic Acid 70 mg Tablets if you are taking any other tablets, you should avoid taking any of your Alendronic Acid 70 mg Tablets and your other medicine

Taking Alendronic Acid 70 mg tablets with food or drink:

- Do not take Alendronic Acid 70 mg tablets if you are pregnant or breast-feeding
- Drinking alcohol: There is no need to avoid alcohol when taking Alendronic Acid 70 mg tablets

3. HOW TO TAKE ALENDRONIC ACID 70 mg TABLETS

Chew Well:

- The medicine is not suitable for people with swallowing difficulties
- Always follow your doctor's instructions and those which are on the pharmacy label. If you do not understand these instructions, ask your doctor or pharmacist.
The following instructions are particularly important to ensure your medicine is effective and to reduce the potential for the medicine to irritate your oesophagus (the tube that connects your mouth with your stomach):

- Choose the day of the week when you will take your tablet that best fits your schedule every week. Take one ALENDRONIC ACID 70 mg Tablet on your chosen day.
- Your medicine should be taken on an empty stomach immediately on rising in the morning. It should be taken with a full glass of plain water (not tea, coffee, mineral water or juice) half an hour before any food, drink or another medication.
- The tablets should be swallowed whole, not chewed or sucked.
- Do not be down on your tablet. You must stay upright (sitting, standing or walking) until you have taken your first meal of the day which must be at least half an hour after the dose of ALENDRONIC ACID 70 mg Tablets.
- Do not take your tablets at bedtime or before getting out of bed.
- If you develop pain or difficulty on swallowing, chest pain or new or worsening heartburn, stop taking ALENDRONIC ACID 70 mg Tablets and contact your doctor.

The usual dosage instructions are given below:

Adults (including the elderly):
One 70 mg tablet once a week.

Children: Not recommended.

If you take more ALENDRONIC ACID 70 mg Tablets than you should:
If you or someone else swallows a lot of the tablets at once, or if you think a child has swallowed any of the tablets, contact your nearest hospital casualty department or your doctor immediately. Give a full glass of milk and do not be down. Overdose can cause:
- Painful muscle cramps, tenderness, weakness, exhaustion and fever.
- It can also cause an upset stomach, vomiting, inflammation and pain in the upper digestive system.

If you forget to take ALENDRONIC ACID 70 mg Tablets:
If you forget to take a tablet, take one on the next morning. Never take two doses together or on the same day. Return to taking one tablet once a week as originally scheduled on your chosen day.


Ref. 12345 A

UK/H/833/01
Module 4

Labelling

Labels on following pages.
Module 5

Scientific discussion during initial procedure

RECOMMENDATION
Based on the review of the data on quality, safety and efficacy, the RMS considered that the application for Alendronic Acid 70mg Tablets in the treatment of post menopausal osteoporosis, could be approved. A national marketing authorisation was granted on 5th July 2005.

EXECUTIVE SUMMARY

This assessment report is based on the assessment report generated under the mutual recognition procedure considering a generic version of Alendronic Acid from Teva UK Ltd. The products were granted marketing authorisations in the UK on 5th July 2005. With the UK as the Reference Member State in this Mutual Recognition Procedure (MRP), the Marketing Authorisation Holder, TEVA UK Limited, applied for marketing authorisations for Alendronic Acid 70mg Tablets in Austria, Belgium, Czech Republic, Denmark, Estonia, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Norway, the Netherlands, Poland, Portugal, Slovak Republic, Slovenia, Spain, Sweden. Day 90 of the Mutual Recognition Procedure was 5th December 2005.

The originator product is Fosamax® Once Weekly 70mg Tablets (Marketing Authorisation Holder: Merck Sharp & Dohme Limited, UK). The original product is listed as Fosamax tablets licensed in June 1993 in Italy. These were the daily tablets with strength of 5mg. The reference medicinal product marketed in the UK is listed as Fosamax Once weekly 70mg tablets (PL 00025/0399 granted November 2000). This licence was an abridged complex of Fosamax 10mg tablets (PL 00025/0326 granted July 1995).

About the product
Alendronate sodium is a bisphosphonate that acts as a specific inhibitor of osteoclast-mediated bone resorption. Bisphosphonates are synthetic analogues of pyrophosphate that bind to the hydroxyapatite found in bone.

The development programme
The objective of the development programme was to formulate a robust, stable, acceptable formulation of Alendronic Acid Tablets comparable in performance to Fosamax Once Weekly Tablets, which is the reference product for this generic application.

General comments on compliance with GMP, GLP, GCP and agreed ethical principles
No new preclinical studies were conducted, which is acceptable given that the application was based on essential similarity to a product that has been licensed for over 10 years.

No clinical efficacy studies were conducted, which is acceptable given that the application was based on essential similarity 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 prior to granting its national authorisation.

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 or 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.

**SCIENTIFIC OVERVIEW AND DISCUSSION**

**Quality aspects**

*Drug substance*

Alendronate sodium as the trihydrate form has a European Pharmacopoeia monograph. The specification for the alendronate sodium monohydrate is taken from the manufacturer’s certificate of analysis, which covers the European pharmacopoeia tests for the trihydrate, with an appropriate modification for the limit on loss on drying. A limit is also included for the solvent used in the manufacturing process; this is in compliance with the guidance on residual solvents. An acceptable particle size specification has also been specified.

An appropriate specification has been provided for the active substance from the finished product manufacturer. The analytic methods are appropriate and an acceptable validation protocol provided.

*Drug product*

The objective of the development programme was to formulate a robust, stable, acceptable formulation of Alendronic Acid Tablets comparable in performance to Fosamax Once Weekly Tablets, which is the reference product for this generic application. Basic tablets and those of the brand leader were investigated and found to be sufficiently comparable. Excipients microcrystalline cellulose, croscarmellose sodium and magnesium stearate comply with the requirements of the European Pharmacopoeia monographs. The product is packed in aluminium-aluminium blisters. Each pack contains 2, 4, 8, 12, 40 and 50 tablets. The packaging materials comply with the European Pharmacopoeia. Neither the active substance nor excipients contain materials of animal origin.

A bioequivalence study has been performed on Alendronic Acid 70mg Tablets versus Fosamax 70mg Tablets. Comparable dissolution and impurity profiles were seen in both products. Based on these data it can be considered that the innovator and the generic product are essentially similar.

The proposed finished product specifications are in compliance with the general pharmacopoeial requirements and the batch data submitted, and are controlled with valid methods. The stability studies on the products have been undertaken on pilot-scale batches packed in packaging proposed for marketing. The tablets have been tested for 6 months at accelerated and 18 months at long-term conditions. Both batches remained within
specifications over the long-term and accelerated periods examined. A shelf-life of 30 months is proposed for this product with no detailed storage instructions. This shelf-life is acceptable.

**Non-clinical aspects**
The assessment report represents an evaluation of the key elements of the information provided by the company in the dossier.

The applicant's expert provides a sufficiently comprehensive overview of the pharmacology and toxicology of alendronic acid. No new preclinical toxicology data were submitted, which is acceptable given the nature of the application.

**Clinical aspects**
The application contains an adequate review of published clinical data. No new toxicology, pharmacokinetic or pharmacodynamic data were submitted for this application and none were required. Data from a single bioequivalence study showed bioequivalence between the two tablets (according to the CPMP criteria).

Regarding safety, no serious or unexpected adverse events were observed in the bioequivalence study and the expert report identifies no new safety issues.

### MODULE 3 - QUALITY

#### PHARMACEUTICAL ASSESSMENT

**ACTIVE INGREDIENT**

Control of active

The active substance has a Drug Master File and a letter of access has been provided.

**DRUG PRODUCT**

Composition

The composition of the tablets is summarised in Table 1. The tablets are white to off-white, flat faced, bevel edged, round, with a “T” on the one side and plain on the other. The tablets are packed into aluminium – aluminium blister packs.

| Table 1 |
| --- | --- | --- | --- |
| **Formulation** | **Quantity mg/tablet** | **Function** | **Reference** |
| Alendronate sodium monohydrate | 81.2 | Drug substance | Ph. Eur. |
| Microcrystalline cellulose | | Diluent & disintegrant | Ph. Eur. |
| Croscarmellose sodium | | Disintegrant | Ph. Eur. |
| Magnesium stearate | | Lubricant | Ph. Eur. |

It is stated that 81.2mg alendronate sodium monohydrate is equivalent to 70mg of alendronic acid
**Pharmaceutical Development**

Formulation development

Compatibility of alendronate sodium monohydrate with the excipients has been assumed on the basis that they are used in the reference product. The excipients are standard and are commonly used in the manufacture of tablets by granulation. The concentrations are within commonly utilised levels. Each of the excipients is also used in the formulation of the reference product.

Manufacturing process development

Pilot batches were manufactured at a scale of 10% of the intended production scale. These were used for the stability study and one was used as the bio-batch. Certificates of analysis have been included for these batches and they comply with the specifications.

**Manufacture**

Production, test control and packaging.

A certificate of GMP has been provided for the production of tablets. A satisfactory GMP Inspection Summary has been provided, following an inspection of the site of manufacture and the appropriate Manufacturers’ licences have also been provided. The batch formula has been presented. This is ten times the batch size produced in the pilot scale batches. A satisfactory description of the details of the manufacturing process has been provided. In process controls have also been described and are acceptable. Description and limits have been presented for the production and control of tablets and are acceptable. All limits have been justified with supporting data. Production-scale validation data has been provided.

**Control of materials**

**Control of excipients**

Microcrystalline cellulose, croscarmellose sodium and magnesium stearate have monographs in the Ph. Eur. Acceptable certificates of analysis have been provided from the finished product manufacture and the excipient manufacturer. The magnesium stearate is from a vegetable source. Product specification has been supplied and validated.

**Analytical and Validation procedures**

All the details have been provided for the Pharmacopoeia and non-pharmacopoeia methods. The methods for assay and impurities and related degradation products are both HPLC methods. The dissolution test uses the HPLC assay method for analysis. The assay for alendronate sodium monohydrate has been validated and linearity has been demonstrated over the appropriate range. The method has been shown to be accurate and precise.

Specificity has been shown by forced degradation using heat, light, oxidation and pH. Robustness has been demonstrated. The assay for impurities and degradation products has been validated. The method has been shown to be accurate and precise. The detection limit was determined. and the quantitation limit. Specificity has been shown in relation to the alendronate peak, placebo and other potential impurities under stressed conditions. Robustness has been demonstrated. The assay has been validated in relation to its use in the
dissolution method. Linearity has been demonstrated over the range 50 to 130% of the nominal working concentration. The method has been shown to be accurate and precise. Specificity has been shown in relation to placebo. Robustness has been demonstrated. Data has been presented to demonstrate the validity of the microbiology methods.

**Batch analyses**

Certificates of analysis have been provided for the batches produced at pilot scale. During the national assessment, the applicant changed the finished product specification at the request of the pharmaceutical assessor. The batch analyses results for all batches tested comply with the revised finished product specification.

**Container closure system**

The packaging consists of aluminium-aluminium blisters. Certificates of analysis are included from the finished product manufacturer, accompanied by certificates of compliance and specification from the manufacturer. Certification has been supplied by the manufacturer of the packaging materials that the PVC is in compliance with the European Pharmacopoeia monograph. Confirmation of compliance to the directives on contact materials have also been supplied.

**Stability**

Stability data has been provided for pilot scale batches packed in the aluminium-aluminium blisters under standard storage conditions. Long term testing is planned up to 36 months and accelerated testing up to 6 months. The samples were tested for appearance, assay, dissolution, impurities/degradation products and microbial count. The methods used are those used on release.

Dissolution profiles and individual tablet data have been provided for the stability studies performed. The individual tablet data has low relative standard deviations, with the percentage release comparable after 19 months compared to the initial. Representative chromatograms have been provided.

The data presented for both batches remains in specification general storage conditions. On the basis of this a shelf life of 30 months has been proposed with no detailed storage conditions. This is acceptable.

**Bioanalytical methods**

The analytical method has been provided, along with a brief summary and the validation report. Analysis of the active substance was shown to be specific and the assay was robust for samples extracted from urine samples.

**Bioavailability/Bioequivalence**

See Clinical Assessment

4. **PRODUCT LITERATURE**

The SPC, PIL and labels are satisfactory.
5. ADMINISTRATIVE
5.1 MAA form
This is satisfactory

5.2 Quality overall summary

6. CONCLUSIONS AND ADVICE
A marketing authorisation was granted
MODULE 4
NON-CLINICAL ASSESSMENT

I INTRODUCTION
The product is a tablet containing 70 mg of alendronate as the sodium monohydrate for oral ingestion and is intended for once-weekly dosing for the treatment of osteoporosis. Alendronate is a bisphosphonate, a class that has a strong affinity for bone, and is a potent inhibitor of bone resorption \textit{in vitro}, \textit{in vivo} and in hypercalcaemia of malignancy. It binds to hydroxyapatite on bone resorption surfaces and inhibits osteoclast-mediated bone resorption. The recommended dose of one 70 mg tablet per week equates to 0.2 mg/kg/day in a 50 kg human.

I.1 Good Laboratory Practice (GLP) aspects
No preclinical studies have been submitted and the applicant has claimed an exemption under Article 10.1(a) (iii) of Council Directive 2001/83/EC. The expert has not discussed any published articles so the question of GLP is not applicable.

II PHARMACODYNAMICS / PHARMACOKINETICS / TOXICOLOGY
The nonclinical overview does not contain an assessment of the animal pharmacodynamics, pharmacokinetics or toxicity studies, nor are there any supporting papers provided. Since the properties of alendronate have been characterised in previous submissions, they will not be repeated here. The expert has reviewed the bioequivalence data and the impurity profile, and is of the view that bioequivalence has been demonstrated in terms of urinary excretion of alendronate. This is discussed further in the clinical assessment report.

The applicant has provided a sufficient justification for the use of the monohydrate rather than the trihydrate form of alendronate sodium in the production of the finished product.

III EXCIPIENTS / DEGRADANTS / IMPURITIES
The excipients are all commonly used in tablet formulations and comply with European Pharmacopoeial standards. They are also all used in the reference product, which, in addition, contains lactose.

The impurity limits are in line with the European Pharmacopoeial values and the residual solvent ethanol is controlled at below the level stipulated in the Note for Guidance on Impurities, Residual Solvents, (CPMP/ICH/283/95). The release and shelf-life specifications are also satisfactory.

The expert has also drawn up a comparison of impurity profiles between alendronate sodium monohydrate, Teva Alendronate Tablets and the reference products cited in a series of European submissions. The comparison showed that:

- in all batches of the active substance, the impurities were less than 0.8%
- there was no degradation of the Teva formulation during the manufacturing process
- the European reference products are similar to one another and have similar levels of impurities to the Teva formulation
The applicant has stated that the active substance is highly soluble and that solubility is not affected by pH. With regard to the propensity for alendronic acid to cause oesophageal irritation, these characteristics are considered to offer a similar degree of risk towards local toxicity as the reference product. Disintegration testing, according to the European Pharmacopoeia method, demonstrates that the applicant’s product disintegrates faster than the reference product. Supporting dissolution data show complete dissolution in 15 minutes for both the applicant’s and reference products. It has also been stated that the applicant’s product is smaller in size than the reference product. These factors show that the applicant’s product is equivalent to the reference product when regarding qualitative differences and their propensity to cause local toxicity.

V SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

The SPC is satisfactory.

VI CONCLUSION

A product licence was granted.
1. **INTRODUCTION**
   The national abridged application claims essential similarity to Fosamax tablets (70mg once weekly).

2. **BACKGROUND**
   Alendronate is a bisphosphonate indicated for the treatment and prophylaxis of osteoporosis.

3. **INDICATIONS**
   Satisfactory. Fully consistent with originator product.

4. **DOSE & DOSE SCHEDULE**
   Satisfactory. Fully consistent with originator product.

5. **CLINICAL PHARMACOLOGY**
   (a) Comparative, randomised, single-dose, 3-way crossover, comparative bioavailability study of test alendronate 70mg tablets and cross-reference Fosamax 70mg tablets under fasting conditions.
   (b) Comparative bioavailability study of test 70mg alendronate tablets and test Fosamax 10mg x7 under fasting conditions.

   This was an open-label randomised single-dose 3-way crossover study in 120 healthy adult males. Each group was 40 subjects and 118 completed the study. Subjects completed a 36-hour cumulative urine collection after dosing. Doses in all periods were separated by a washout of 7 days.

   \( R_{\text{max}} \) and \( t_{\text{max}} \) were calculated for alendronate in urine. Pharmacokinetic results for \( \text{Tae (0-36)} \) and \( R_{\text{max}} \) are presented overleaf.

   **Results:**
   Ratios of LSM (90% Confidence Intervals)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TEVA (1 x 70mg) (A) vs Merck (1 x 70mg) (B)</th>
<th>TEVA (1 x 70mg) (A) vs Merck (7 x 10mg) (C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{Tae (0-36)} )</td>
<td>105.7% (97.0-115.1%)</td>
<td>100.8% (92.6-109.8%)</td>
</tr>
<tr>
<td>( R_{\text{max}} )</td>
<td>106.5% (97.5-116.3%)</td>
<td>99.9% (91.5-109.1%)</td>
</tr>
</tbody>
</table>

   **Assessor's comments:** The applicant has justified the use of urinary data as a surrogate for plasma data in this specific study. The results from this study show that bioequivalence can be demonstrated between Teva and Fosamax 70mg Tablets. This is further supported by the biopharmaceutical characteristics (solubility of drug substance and dissolution results of the tablets).

6. **EFFICACY**
   No new data.
7. **SAFETY**
No new data.

8. **EXPERT REPORTS**
Satisfactory.

9. **PATIENT INFORMATION LEAFLET (PIL)**
Satisfactory. Fully consistent with originator product.

10. **LABELLING**
Satisfactory.

11. **APPLICATION FORM (MAA)**
Satisfactory.

12. **SUMMARY OF PRODUCT CHARACTERISTICS (SPC)**
Satisfactory. Fully consistent with originator product.

13. **MEDICAL CONCLUSION**
A marketing authorisation was granted.