IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA1330/002/001
Case No: 2040878

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Gedeon Richter Ltd

H-1103 Budapest, **Gyomroi ut 19-21**, **Hungary**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Alendronic Acid 70mg "once weekly" film-coated tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **22/01/2008** until **18/12/2012**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Alendronic Acid 70mg "once weekly" film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 70mg alendronic acid (equivalent to 91.35 mg sodium alendronate trihydrate).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film coated tablet.
White, round, biconvex film-coated tablet with engraving “M14”.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of post menopausal osteoporosis. Alendronate reduces the risk of vertebral and hip fractures.

4.2 Posology and method of administration

The recommended dosage is one70mg film-coated tablet once weekly for oral use.

To permit adequate absorption of alendronate:

Alendronic Acid 70mg „once weekly” must be taken on an empty stomach at least 30 minutes before the first food, drink or medicinal product of the day with plain water only. Other beverages (including mineral water either still or sparkling), food and some medicinal products are likely to reduce the absorption of alendronate (see section 4.5).

In order to reduce the potential for local and oesophageal irritation/adverse experiences the following should be done:

- Alendronic Acid 70mg „once weekly” should be swallowed upon arising for the day with a full glass of water (not less than 200ml).
- Patients should not chew the tablet or allow the table to dissolve in their mouths.
- 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 70mg „once weekly”.
- Alendronic Acid 70mg „once weekly” should not be taken at bedtime or before arising for the day.
- Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate (see section 4.4).

Use in the elderly: No dosage adjustment is necessary for the elderly.

Use in renal impairment: No dosage adjustment is necessary for patients with glomerular filtration rate (GFR) greater than 35 ml/min. Due to lack of experience alendronate is not recommended for patients with renal impairment where GFR is less than 35 ml/min.

Use in children: There is no relevant indication for use of Alendronic Acid 70mg „once weekly" in children.

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 the active substance or to any of the excipients.
- Hypocalcaemia
- See also section 4.4.

4.4 Special warnings and precautions for use

Alendronate 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 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 gastrointestinal disease such as pepticulcer, or active gastro-intestinal 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 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 (postmarketing) reports of gastric and duodenal ulcers, some severe and with complications. Acausal relationship cannot be ruled out.

Osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection (including osteomyelitis) has been reported in patients with cancer receiving treatment regimens including primarily intravenously administered bisphosphonates. Many of these patients were also receiving chemotherapy and corticosteroids. Osteonecrosis of the jaw has also been reported inpatients 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).

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 postmarketing experience, these symptoms have rarely been severe and/or incapacitating (see '4.8 Undesirable effects'). The time to onset of symptoms varied from one day to several months after starting treatment. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.

Patients should be instructed that if they miss a dose of Alendronic Acid 70mg „once weekly" 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 'Contraindications'). 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 hypocalcemia should be monitored during therapy with Alendronic Acid 70mg „once weekly".
Due to the 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 rare reports of symptomatic hypocalcemia, which have occasionally been severe and often occurred in patients with predisposing conditions (e.g.hypoparathyroidism ,vitamin D deficiency and calcium malabsorption).

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

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 30minutes after taking alendronate before taking any other oral medicinal product.

No interaction studies have been performed. However, 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

Use during pregnancy

There are no adequate data from the use of alendronic acid in pregnant women. Animal studies do not indicate direct harmful effects with respect to pregnancy, embryonal/fetal development, or postnatal development. Alendronic acid given during pregnancy in rats caused dystocia related to hypocalcaemia (see section 5.3). Given the indication, alendronic acid should not be used during pregnancy.

Use during lactation

It is not known whether alendronic acid is excreted into human breast milk. Given the indication, alendronic acid 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 postmenopausal women with osteoporosis the overall safety profiles of Alendronic acid 70mg/week (n=519) and alendronate 10mg/day (n=370) were similar. In two threeyear studies of virtually identical design, in postmenopausal women (alendronate 10mg: n=196, placebo: n=397) the overall safety profiles of alendronate 10mg/day and placebo were similar.

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

	One-Year Study		*Three-Year Study*	
	Alendronic acid 70mg (n = 519) %	*Alendronate 10mg/day (n=370) %*	*Alendronate 10mg/day (n=196) %*	*Placebo (n = 397) %*
Gastro-intestinal				
abdominal pain	*3.7*	*3.0*	*6.6*	*4.8*
dyspepsia	*2.7*	*2.2*	*3.6*	*3.5*
acid regurgitation	*1.9*	*2.4*	*2.0*	*4.3*
nausea	*1.9*	*2.4*	*3.6*	*4.0*
abdominal distention	*1.0*	*1.4*	*1.0*	*0.8*
constipation	*0.8*	*1.6*	*3.1*	*1.8*
diarrheoa	*0.6*	*0.5*	*3.1*	*1.8*
dysphagia	*0.4*	*0.5*	*1.0*	*0.0*
flatulence	*0.4*	*1.6*	*2.6*	*0.5*
gastritis	*0.2*	*1.1*	*0.5*	*1.3*
gastric ulcer	*0.0*	*1.1*	*0.0*	*0.0*
oesophageal ulcer	*0.0*	*0.0*	*1.5*	*0.0*
Musculoskeletal				
musculoskeletal (bone, muscle or joint) pain	*2.9*	*3.2*	*4.1*	*2.5*
muscle cramp	*0.2*	*1.1*	*0.0*	*1.0*
Neurological				
headache	*0.4*	*0.3*	*2.6*	*1.5*

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

[Common (≥1/100,<1/10), Uncommon (≥1/1000,<1/100), Rare (≥1/10,000,<1/1000), Very rare (<1/10,000 including isolated cases)]

Immune system disorders:
Rare: hypersensitivity reactions including urticaria and angioedema
Metabolism and nutrition disorders:
Rare: symptomatic hypocalcaemia, often in association with predisposing conditions. (see section 4.4)
Nervous system disorders:
Common: headache

Eye disorders:
Rare: uveitis, scleritis, episcleritis

Gastrointestinal disorders:
Common: abdominal pain, dyspepsia, constipation, diarrhoea, flatulence, oesophageal ulcer*, dysphagia*, abdominal distension, acid regurgitation
Uncommon: nausea, vomiting, gastritis, oesophagitis*, oesophageal erosions*, melena
Rare: oesophageal stricture*, or opharyngeal ulceration*, upper gastrointestinal PUBs (perforation, ulcers, bleeding) (see section 4.4)* See sections 4.2 and 4.4
Skin and subcutaneous tissue disorders:
Uncommon: rash, pruritus, erythema

Rare: rash with photosensitivity Very rare and isolated cases: isolated cases of severe skin reactions including Stevens Johnson syndrome and toxic epidermal necrolysis

Musculoskeletal, connective tissue and bone disorders:
Common: musculoskeletal (bone, muscle or joint) pain

Rare: Osteonecrosis of the jaw has been reported in patients treated by bisphosphonates. The majority of the reports refer to cancer patients, but such cases have also been reported in patients treated for osteoporosis. Osteonecrosis of the jaw is generally associated with tooth extraction and/or local infection (including osteomyelitis). Diagnosis of cancer, chemotherapy, radio therapy, corticosteroids and poor oral hygiene are also deemed as risk factors; severe musculoskeletal (bone, muscle or joint) pain (see 4.4 ‘Special warnings and precautions for use’).

General disorders and administration site conditions:
Rare: transient symptoms as in an acutephase response (myalgia, malaise and rarely, fever), typically in association with initiation of treatment.

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 10mg/day versus approximately 12 and 3% of those taking placebo. However, the incidences of decreases in serum calcium to <8.0mg/dl (2.0mmol/l) and serum phosphate to ≤2.0mg/dl (0.65mmol/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 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 (standing or sitting).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs affecting bone structure and mineralization**,** bisphosphonate ATC Code: M05BA04

The active substance alendronic acid, is a bisphosphonate that inhibits osteoclastic bone resorption with no direct effect on bone formation. Preclinical studies have demonstrated a preference for localization of alendronate to sites *where active resorption takes place*. 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.

5.2 Pharmacokinetic properties

Absorption:
The oral mean bioavailability of alendronate in women was 0.64% for doses ranging from 5 to 70mg when administered after an overnight fast and two hours before a standardized 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 standardized breakfast.

Concomitant administration of alendronate with coffee or orange juice reduced bioavailability by approximately 60%.

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

Distribution:
Alendronate transiently distributes to soft tissues following administration but is then rapidly redistributed to bone or excreted in the urine. Protein binding in human plasma is approximately 78%.

Metabolism:
There is no evidence that alendronate is metabolized in animals or humans.

Elimination:
Following a single intravenous dose of [^{14}C] alendronate intravenous administration, approximately 50% of the dose was excreted in the urine within 72 hours. No active substance was recovered in the faeces. Following a single 10mg intravenous dose, the renal clearance of alendronate was 71ml/min, and systemic clearance did not exceed 200ml/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, and thus it is not anticipated to interfere with the excretion of other medicinal products by those systems in humans.

Characteristics in patients:
The drug that is absorbed but 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 35mg/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 section 4.2.

5.3 Preclinical safety data

Nonclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.
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 fetal ossification. The relevance to humans is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Cellulose microcrystalline (E460)
Colloidal anhydrous silica
Croascarmellose sodium (E468)
Magnesium stearate (E572)

Film-coating:
Lustre Clear LC103:
Cellulose microcrystalline (E460)
Carrageenan (E407)
Macrogol 8000

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years.

6.4 Special precautions for storage

Store below 25ºC.

6.5 Nature and contents of container

2 film-coated tablets are packed into OPA/Al/PVC/Al blister and folded carton.

4 filmcoated tablets are packed into OPA/Al/PVC/Al blister and folded carton.

12 (3x4) filmcoated tablets are packed into OPA/Al/PVC/Al blisters and folded carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Gedeon Richter Ltd.
H-1103 Budapest
Gyömrői út 1921
Hungary

8 MARKETING AUTHORISATION NUMBER

PA 1330/2/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19th December 2007

10 DATE OF REVISION OF THE TEXT