IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0126/148/001
Case No: 2052541

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

Clonmel Healthcare Limited

Waterford Road, **Clonmel**, **Co. Tipperary**, **Ireland**

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

Osteomel 10 mg 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 **16/09/2008** until **08/09/2010**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Osteomel 10 mg Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For excipients see 6.1.

3 PHARMACEUTICAL FORM

Tablet.

White to off-white, capsule-shaped tablet, embossed “AN 10” on one side and “Arrow logo” on the other.

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

For oral use only.

The recommended dosage is 10 mg once daily.

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

To assist delivery to the stomach and thus reduce the risk of irritation/side effects locally and in the oesophagus (see Section 4.4 Special warnings and precautions for use)

- Osteomel tablets should only be swallowed on arising for the day with a whole glass of water (not less than 200 ml or 7 fl. oz).
- Osteomel tablets should be swallowed whole. The tablets should not be chewed, sucked or allowed to dissolve in the mouth on account of the risk of oropharyngeal ulceration.
- Patients should not lie down until after the first meal of the day, which must be at least 30 minutes after taking the tablet.
- Patients should not lie down within 30 minutes of taking Osteomel 10 mg tablets.
- Osteomel 10 mg tablets should not be taken at bedtime or before arising for the day.

Patients should be given a calcium and vitamin D supplement if the diet is inadequate (see Section 4.4 Special warnings and precautions for use).

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

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

Use in impaired hepatic function
No dose adjustment is necessary.

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

4.3 Contraindications

- Oesophageal abnormalities and other factors that delay oesophageal emptying, such as stricture or achalasia.
- Inability to stand or sit upright for at least 30 minutes.
- Hypersensitivity to alendronate, other bisphosphonates or to any of the excipients.
- Hypocalcaemia.

See also Section 4.4 Special warnings and precautions for use.

4.4 Special warnings and precautions for use

Alendronate can cause local irritation to the upper gastrointestinal mucosa. As there is a risk of worsening of the underlying disease, caution should be observed if alendronate is given to patients with active upper gastrointestinal tract problems, such as dysphagia, oesophageal disease, gastritis, duodenitis or ulcers, or in cases of recent (during the last year) severe gastrointestinal disease such as gastric ulcer, active gastrointestinal bleeding or surgery in the upper gastrointestinal tract other than pyloroplasty (see Section 4.3 Contraindications).

Oesophageal side effects (in some cases severe and requiring hospitalisation) such as oesophagitis, oesophageal ulcers or oesophageal erosions, in rare cases followed by oesophageal stricture, have been reported in patients receiving treatment with alendronate. The physician should therefore be alert to any signs or symptoms of possible oesophageal reaction. The patients should be instructed to discontinue alendronate and seek medical attention if they develop symptoms of oesophageal irritation such as dysphagia, pain on swallowing, retrosternal pain or new/worsened heartburn.

The risk of severe oesophageal side effects is thought to be greater in patients who do not take alendronate correctly and/or continue to take alendronate after developing symptoms indicative of oesophageal irritation. It is very important that complete administration instructions are given to, and understood, by the patient (see Section 4.2 Posology and method of administration). Patients should be informed that the risk of oesophageal problems may increase if they do not follow these instructions.

Despite no increased risk having been observed in extensive clinical trials, following marketing of the original preparation there have been reports of rare cases of gastric and duodenal ulcers, some of them severe and with complications. A causal relationship cannot be excluded (see Section 4.8 Undesirable effects).

Alendronate is not recommended for patients with impaired renal function if the GFR is less than 35 ml/min (see Section 4.2 Posology and method of administration).

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

Hypocalcaemia must be corrected before treatment with alendronate is initiated (see Section 4.3 Contraindications). Other disorders of mineral metabolism (such as vitamin D deficiency and hypoparathyroidism) should also be effectively treated before starting alendronate. In patients with these conditions, serum calcium and symptoms of hypocalcaemia should be monitored during treatment with alendronate.

On account of the positive effects of alendronate on the increase in bone mineralisation, reductions in serum calcium and serum phosphate may occur. These are usually slight and asymptomatic. However, in rare cases, symptomatic hypocalcaemia has been reported which occasionally has been severe and often occurred in patients with predisposing conditions (e.g. hypoparathyroidism, vitamin D deficiency and in cases of calcium malabsorption). It is therefore particularly important to ensure that patients taking glucocorticoids have an adequate calcium and vitamin D intake.

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

A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, chemotherapy, radiotherapy, corticosteroids, poor oral hygiene).

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.

Osteomel 10 mg Tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

If taken at the same time, it is likely that foods and drinks (including mineral water), calcium supplements, antacids and some oral medicines will affect the absorption of alendronate. Patients must therefore wait for at least 30 minutes after taking alendronate before taking any other oral medicine (see Section 4.2 Posology and method of administration).

No other clinically significant drug interactions are expected. A number of patients in the clinical trials received oestrogen (intravaginally, transdermally or orally) concomitantly with alendronate. No undesirable effects could be related to the combination treatment.

No specific interaction studies have been carried out, but alendronate was used in clinical trials concomitantly with a number of other commonly prescribed medicines without any evidence of clinically unfavourable interactions.

4.6 Pregnancy and lactation

Use during pregnancy
There are insufficient data regarding the use of alendronate in pregnant women. Animal studies revealed effects on foetal bone formation at high doses. Alendronate given to pregnant rats caused hypocalcaemia-related dystocia (see Section 5.3 Preclinical safety data). In view of the indication, alendronate should not be used during pregnancy.

Use during lactation
It is not known whether alendronate is excreted into breast milk in humans. In view of the indication, alendronate should not be used by breast-feeding women.

4.7 Effects on ability to drive and use machines

Osteomel 10mg tablets have no influence on the ability to drive and use machines.

4.8 Undesirable effects

In two three-year studies of almost identical design, with post-menopausal women (alendronate 10 mg: n=196; placebo: n= 397) the overall safety profiles for alendronate 10 mg daily and placebo were similar.

Undesirable effects reported by the investigators as possibly, probably or definitely related to the drug are presented below if they occurred in ≥ 1 % of any in the treatment groups in the one-year study or in ≥ 1 % of the patients who were treated with alendronate 10 mg per day and with an incidence higher than in patients who were treated with placebo in three-year studies.

	Three-year studies	
	Alendronate10 mg daily (n=196) %	**Placebo (n=397) %**
Gastrointestinal		
Abdominal pain	6.6	4.8
Dyspepsia	3.6	3.5
Acid regurgitation	2.0	4.3
Nausea	3.6	4.0
Abdominal distension	1.0	0.8
Constipation	3.1	1.8
Diarrhoea	3.1	1.8
Dysphagia	1.0	0.0
Flatulence	2.6	0.5
Gastritis	0.5	1.3
Gastric ulcer	0.0	0.0
Oesophageal ulcer	1.5	0.0
Musculoskeletal		
Musculoskeletal pain (bone, muscle or joints)	4.1	2.5
Muscle cramps	0.0	1.0
Neurological		
Headache	2.6	1.5

The following undesirable effects have also been reported in clinical trials and/or post marketing:

Nervous system disorders
Common (≥1/100, <1/10): Headache

Eye disorders
Rare (≥1/10,000, <1/1000): Uveitis, scleritis

Gastrointestinal disorders
Common (≥1/100, <1/10): Abdominal pain, dyspepsia, constipation, diarrhoea, flatulence, oesophageal ulcers*, dysphagia*, abdominal distension, acid regurgitation.
Uncommon (≥1/1000, <1/100): Nausea, vomiting, gastritis, oesophagitis* oesophageal erosions*, melaena.
Rare (≥1/10,000, <1/1000): Oesophageal stricture*, oropharyngeal ulceration*, upper gastrointestinal PUB (perforations, ulcers, bleeding), a causal relationship cannot be ruled out.

Skin and subcutaneous tissue disorders
Very rare (≤1/10,000): Isolated cases of severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported.

Musculoskeletal, connective tissue and bone disorders
Common (≥1/100, <1/10): Musculoskeletal pain (bones, muscles or joints)
Unknown frequency: Osteonecrosis

General disorders and administration site conditions
Uncommon (≥1/1000, <1/100): Rash, pruritus, erythema.
Rare (≥1/10,000, <1/1000): Hypersensitivity reactions including urticaria and angioedema. Transient symptoms as in an acute phase reaction (myalgia, malaise and in rare cases fever) usually in connection with the start of treatment. Skin rash with photosensitivity. Symptomatic hypocalcaemia, generally in connection with predisposing conditions (see. Section 4.4 Special warnings and precautions for use).

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

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 osteomyelistis). Diagnosis of cancer, chemotherapy, radiotherapy, corticosteroids and poor oral hygiene are also deemed as risk factors (see section 4.4 Special warnings and precautions for use).

Laboratory values
In clinical trials, asymptomatic, slight and transient decreases in serum calcium and serum phosphate were observed in approx. 18 and 10 % respectively of the patients taking alendronate 10 mg/day versus 12 and 3 % respectively of those taking placebo. However, the incidence of reductions in serum calcium to <2.0 mmol/l and serum phosphate to ≤0.65 mmol/l was comparable in the two groups.

4.9 Overdose

Hypocalcaemia, hypophosphataemia and upper gastrointestinal side effects such as upset stomach, heartburn, oesophagitis, gastritis or ulcer can occur on oral overdosage. There is no specific information available with regard to overdosage with alendronate. Milk or antacids should be given in order to bind alendronate. On account of the risk of oesophageal irritation, vomiting should not be induced and the patient should be kept in an upright position.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for treatment of bone diseases, bisphosphonates.

ATC code: M05BA04

The active substance in Osteomel 10 mg tablets, alendronate sodium trihydrate, is a bisphosphonate that inhibits osteoclastic bone resorption without any direct effect on bone formation. Preclinical studies have demonstrated a preference for localisation of alendronate to sites where active resorption takes place. Osteoclastic activity is inhibited, but formation and binding of the osteoclasts is not affected. Bone formed during treatment with alendronate is of normal quality.

Treatment of post-menopausal osteoporosis.

Osteoporosis is defined as bone mineral density (BMD) of the spine or hip 2.5 standard deviations below the mean value of a normal young population or as a previous fragility fracture, irrespective of bone mineral density.

The effects of alendronate on BMD and fracture incidence in post-menopausal women were studied in two initial efficacy studies of identical design (n=994), and in the Fracture Intervention Trial (FIT: n=6459).

In the initial efficacy studies, the increases in BMD with alendronate 10 mg daily relative to placebo after three years were 8.8 %, 5.9 % and 7.8 % at the spine, femoral neck and trochanter respectively. Total BMD also increased significantly. In the patients treated with alendronate, the proportion of patients who suffered one or more vertebral fractures was reduced by 48 % (alendronate 3.2 % versus placebo 6.2 %). In the two-year extensions of these studies the BMD in the spine and trochanter continued to increase. In addition, BMD at the femoral neck and total body was maintained.

The FIT study included two placebo-controlled trials in which alendronate was given daily (5 mg daily for two years and 10 mg daily for a further one or two years).

- FIT 1: A three-year study with 2027 patients who had 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 % versus placebo 15.0 %). In addition, a statistically significant reduction in the incidence of hip fractures was confirmed (1.1 % versus 2.2 %, a reduction of 51 %).
- FIT 2: A four-year study with 4432 patients who had a low bone mass but had not had any vertebral fracture at the start of the study. In this study, in a subgroup analysis of osteoporotic women (37 % of the total population who fulfilled the definition of osteoporosis given above) a significant difference was seen in the incidence of hip fractures (alendronate 1.0 % versus placebo 2.2 %, a reduction of 56 %) and in the incidence of ≥1 vertebral fracture (2.9 % versus 5.8 %, a reduction of 50 %).

5.2 Pharmacokinetic properties

Absorption
Compared with an intravenous reference dose, the mean oral bioavailability of alendronate in women was 0.64 % for doses ranging from 5 to 70 mg given after an overnight fast and two hours before a standardised breakfast. Bioavailability decreased to an estimated 0.46 % and 0.39 % when alendronate was given an hour or half an hour before a standardised breakfast.
In osteoporosis studies alendronate was effective when it was given at least 30 minutes before the first meal or drink of the day. Bioavailability was negligible irrespective of whether alendronate was given together with or up to two hours after a standardised breakfast. Concomitant administration of alendronate with coffee or orange juice reduced bioavailability by approx. 60 %. In healthy persons, oral prednisolone (20 mg three times daily for five days) did not result in any clinically meaningful change in the oral bioavailability of alendronate (a mean increase ranging from 20 % to 44 %).

Distribution
Studies in rats show that alendronate is initially distributed to soft tissues after intravenous administration of 1 mg/kg, but is then rapidly redistributed to the skeleton 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 (^{14}C) 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 intravenous dose of 10 mg, 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 6 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 thought to interfere with the excretion of other drugs by those systems in humans.

Characteristics in patients
Preclinical studies show that the drug that is not deposited in bone is rapidly excreted in the urine. No evidence of saturation of bone uptake was found after chronic dosing with cumulative 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 Section 4.2 Posology and method of administration).

5.3 Preclinical safety data

Conventional studies of general toxicity, genotoxicity and carcinogenicity did not reveal any special risks for humans. Studies in female rats showed that treatment with alendronate during pregnancy was associated with dystocia during parturition, which was related to hypocalcaemia. Studies in which rats were given high doses showed an increased incidence of incomplete foetal bone formation. The relevance for humans is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Lactose monohydrate
Croscarmellose sodium
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years.

6.4 Special precautions for storage

Do not store above 25°C.

Store in the original package.

6.5 Nature and contents of container

The tablets are supplied in triplex blister (PVC/PE/PVDC/AL) packaging.

14, 28, 56, 98, 112 and 50 x 1 (unit dose).

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

Clonmel Healthcare Ltd
Waterford Road
Clonmel
Co. Tipperary

8 MARKETING AUTHORISATION NUMBER

PA 0126/148/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 9th September 2005

10 DATE OF REVISION OF THE TEXT

February 2007