

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Alendronic Acid Aurobindo 10mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

White to off-white, round, biconvex, uncoated tablets debossed with 'F' on one side and '18' on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

In post-menopausal women with osteoporosis, Alendronic Acid Aurobindo is indicated for the treatment of osteoporosis to prevent fractures, including those of the hip and spine (vertebral compression fractures).

Alendronic Acid Aurobindo is indicated for the treatment of osteoporosis in men to prevent fractures.

Alendronic Acid Aurobindo

is indicated for the treatment and prevention of glucocorticoid-induced osteoporosis in men and women.

In post-menopausal women who are at risk of developing osteoporosis Alendronic Acid Aurobindo is indicated for the prevention of osteoporosis to reduce the risk of future fracture.

4.2 Posology and method of administration

Treatment of osteoporosis in postmenopausal women

The recommended dose is 10 mg once a day.

Treatment of osteoporosis in men

The recommended dose is 10 mg once a day.

Treatment and prevention of glucocorticoid-induced osteoporosis

For post-menopausal women not receiving hormone replacement therapy (HRT) with an oestrogen, the recommended dosage is 10 mg once a day.

For other patients (i.e. men, pre-menopausal women and post-menopausal women receiving HRT with an oestrogen), the recommended dosage is 5 mg once a day.

Prevention of osteoporosis in post-menopausal women: The recommended dosage is 5 mg once a day.

To permit adequate absorption of alendronic acid:

Alendronic acid must be taken at least 30 minutes before the first food, beverage, or medicinal product of the day with plain water only. Other beverages (including mineral water), food and some medicinal products are likely to reduce the absorption of alendronic acid (see section 4.5).

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

- Alendronic Acid Aurobindo 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 only swallow 'Alendronic Acid Aurobindo' whole. Patients should not crush or 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.

All patients with osteoporosis should receive supplemental calcium and vitamin D if dietary intake is inadequate (see section 4.4).

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

Use in renal impairment: No dosage adjustment is necessary for patients with mild-to-moderate renal insufficiency (creatinine clearance 35-60 ml/min). Alendronic acid is not recommended for patients with more severe renal insufficiency (creatinine clearance <35 ml/min).

Use in hepatic impairment: No dosage adjustment is necessary (see 5.2 'Pharmacokinetic properties', biotransformation).

Paediatric patients: Alendronate sodium is not recommended for use in children under the age of 18 years due to insufficient data on safety and efficacy in conditions associated with paediatric osteoporosis (also see section 5.1).

Clinical experience with 'Alendronic Acid Aurobindo' is available for a period of five years: extension studies are ongoing. The effects of longer-term therapy are unknown.

The optimal duration of bisphosphonate treatment for osteoporosis has not been established. The need for continued treatment should be re-evaluated periodically based on the benefits and potential risks of alendronic acid on an individual patient basis, particularly after 5 or more years of use.

4.3 Contraindications

- Hypersensitivity to the alendronic acid or to any of 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 section 4.4.)

4.4 Special warnings and precautions for use

This product contains a novel drug substance. Any side-effects or adverse drug reactions associated with its use should be reported.

Alendronic acid 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 alendronic acid 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 section 4.3).

In patients with known Barrett's oesophagus, prescribers should consider the benefits and potential risks of alendronic acid on an individual patient basis.

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 section 4.2). Patients should be informed that failure to follow these instructions may increase their risk of oesophageal problems.

While no increased risk was observed in extensive clinical trials, there have been rare (post-marketing) reports of gastric and duodenal ulcers, some severe and with complications.

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, periodontal disease).

While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop osteonecrosis of the jaw while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of the jaw.

Clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates. In post-marketing experience, these symptoms have rarely been severe and/or incapacitating (see section 4.8). The time to onset of symptoms varied from one day to several months after starting treatment. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.

Alendronic acid is not recommended for patients with renal impairment where GFR is less than 35 ml/min, (see section 4.2).

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

Hypocalcaemia must be corrected before initiating therapy with alendronic acid (see section 4.3). 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 alendronic acid.

Due to positive effects of alendronic acid 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.

Atypical fractures of the femur

Atypical subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonate therapy, primarily in patients receiving long-term treatment for osteoporosis. These transverse or short oblique fractures can occur anywhere along the femur from just below the lesser trochanter to just above the supracondylar flare. These fractures occur after minimal or no trauma and some patients experience thigh or groin pain, often associated with imaging features of stress fractures, weeks to months before presenting with a completed femoral fracture. Fractures are often bilateral; therefore the contralateral femur should be examined in bisphosphonate-treated patients who have sustained a femoral shaft fracture. Poor healing of these fractures has also been reported. Discontinuation of bisphosphonate therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient, based on an individual benefit risk assessment.

During bisphosphonate treatment patients should be advised to report any thigh, hip or groin pain and any patient presenting with such symptoms should be evaluated for an incomplete femur fracture.

4.5 Interaction with other medicinal products and other forms of interaction

If taken at the same time, it is likely that 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 medication.

No other drug interactions of clinical significance are anticipated.

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.

Since NSAID use is associated with gastrointestinal irritation, caution should be used during concomitant use with alendronate.

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 Fertility, pregnancy and lactation

Use during pregnancy

Alendronic Acid Aurobindo should not be used during pregnancy. There are no adequate data from the use of alendronate in pregnant women. Animal studies do not indicate direct harmful effects with respect to pregnancy, embryonal/fetal development, or postnatal development. Alendronate given during pregnancy in rats caused dystocia related to hypocalcemia (see 5.3 'Preclinical safety data').

Use during lactation

It is not known whether alendronic acid is excreted into human breast milk. Alendronic Acid Aurobindo should not be used by breast-feeding women.

4.7 Effects on ability to drive and use machines

No studies on the ability to drive and use machines have been performed. However, certain adverse reactions that have been reported with alendronic acid may affect some patients' ability to drive or operate machinery. Individual responses to alendronic acid may vary. (See 4.8 Undesirable effects).

4.8 Undesirable effects

Alendronic Acid Aurobindo has been studied in nine major clinical studies (n=5,886). In the longest running trials in post-menopausal women up to five years experience has been collected. Two years safety data are available in both men with osteoporosis and men and women on glucocorticoids.

The following adverse experiences have also been reported during clinical studies and/or post-marketing use: [Common ($\geq 1/100$, $< 1/10$), Uncommon ($\geq 1/1000$, $< 1/100$), Rare ($\geq 1/10,000$, $< 1/1000$), 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*, oropharyngeal 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, radiotherapy, corticosteroids and poor oral hygiene are also deemed as risk factors; severe musculoskeletal (bone, muscle or joint) pain (see Section 4.4).

General disorders and administration site conditions:

Rare: transient symptoms as in an acute-phase response (myalgia, malaise and rarely, fever), typically in association with initiation of treatment.

During post-marketing experience the following reactions have been reported (frequency unknown):

Nervous system disorders: dizziness, dysgeusia

Ear and labyrinth disorders: vertigo

Skin and subcutaneous tissue disorders: alopecia

Musculoskeletal, connective tissue and bone disorders: joint swelling.

General disorders and administration site conditions: asthenia, peripheral oedema

Laboratory test findings

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

During post-marketing experience the following reactions have been reported (frequency rare):
Atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction)

4.9 Overdose

Significant lethality after single oral doses was seen in female rats and mice at 552 mg/kg (3,256 mg/m²) and 966 mg/kg (2,898 mg/m²) (2,760 and 4,830 times* the recommended dose for the treatment of osteoporosis in post-menopausal women), respectively. In males, these values were slightly higher, 626 and 1,280 mg/kg, respectively.

There was no lethality in dogs at oral doses up to 200 mg/kg (4,000 mg/m²) (1,000 times* the recommended dose for the treatment of osteoporosis in post-menopausal women).

No specific information is available on the treatment of overdosage with alendronic acid. Hypocalcaemia, hypophosphataemia and upper gastro-intestinal adverse events, such as upset stomach, heartburn, oesophagitis, gastritis, or ulcer, may result from oral overdosage. 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.

* Based on a patient weight of 50 kg.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs affecting bone structure and mineralisation, bisphosphonate.

ATC Code: M05B A04

Alendronic acid is a bisphosphonate that inhibits osteoclastic bone resorption with no direct effect on bone formation. The bone formed during treatment with alendronic acid is of normal quality.

Treatment of post-menopausal osteoporosis

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 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: a three-year study of 2,027 patients who had at least one baseline vertebral (compression) fracture and a four-year study of 4,432 patients with low bone mass but without a baseline vertebral fracture, 37% of whom had osteoporosis as defined by a baseline femoral neck BMD at least 2.5 standard deviations below the mean for young, adult women. In all FIT patients with osteoporosis from both studies, alendronic acid reduced the incidence of: ≥ 1 vertebral fracture by 48%, multiple vertebral fractures by 87%, ≥ 1 painful vertebral fracture by 45%, any painful fracture by 31% and hip fracture by 54%.

Overall these results demonstrate the consistent effect of alendronic acid to reduce the incidence of fractures, including those of the spine and hip, which are the sites of osteoporotic fracture associated with the greatest morbidity.

Prevention of post-menopausal osteoporosis

The effects of alendronic acid to prevent bone loss were examined in two studies of post-menopausal women aged ≤ 60 years. In the larger study of 1,609 women (≥ 6 months post-menopausal) those receiving alendronic acid 5 mg daily for two years had BMD increases of 3.5%, 1.3%, 3.0% and 0.7% at the spine, femoral neck, trochanter and total body, respectively. In the smaller study (n=447), similar results were observed in women (6 to 36 months post-menopausal) treated with alendronic acid 5 mg daily for three years. In contrast, in both studies, women receiving placebo lost bone mass at a rate of approximately 1% per year.

The longer term effects of alendronic acid in an osteoporosis prevention population are not known but clinical trial extensions of up to 10 years of continuous treatment are currently in progress.

Concomitant use with oestrogen/hormone replacement therapy (HRT)

The effects on BMD of treatment with alendronic acid 10 mg once-daily and conjugated oestrogen (0.625 mg/day) either alone or in combination were assessed in a two-year study of hysterectomised, post-menopausal, osteoporotic women. At two years, the increases in lumbar spine BMD from baseline were significantly greater with the combination (8.3%) than with either oestrogen or alendronic acid alone (both 6.0%).

The effects on BMD when alendronic acid was added to stable doses (for at least one year) of HRT (oestrogen ± progestin) were assessed in a one-year study in post-menopausal, osteoporotic women. The addition of alendronic acid 10 mg once-daily to HRT produced, at one year, significantly greater increases in lumbar spine BMD (3.7%) vs. HRT alone (1.1%).

In these studies, significant increases or favourable trends in BMD for combined therapy compared with HRT alone were seen at the total hip, femoral neck and trochanter. No significant effect was seen for total body BMD.

Treatment of osteoporosis in men

The efficacy of alendronic acid 10 mg once daily in men (ages 31 to 87; mean, 63) with osteoporosis was demonstrated in a two-year study. At two years, the mean increases relative to placebo in BMD in men receiving alendronic acid 10 mg/day were: lumbar spine, 5.3%; femoral neck, 2.6%; trochanter, 3.1%; and total body, 1.6%. Alendronic acid was effective regardless of age, race, gonadal function, baseline rate of bone turnover, or baseline BMD. Consistent with much larger studies in post-menopausal women, in these men, alendronic acid 10 mg/day reduced the incidence of new vertebral fracture (assessed by quantitative radiography) relative to placebo (0.8% vs. 7.1%) and, correspondingly, also reduced height loss (-0.6 vs. -2.4mm).

Glucocorticoid-induced osteoporosis

The efficacy of alendronic acid 5 and 10 mg once-daily in men and women receiving at least 7.5 mg/day of prednisone (or equivalent) was demonstrated in two, one-year studies. At one year, the mean increases relative to placebo in BMD in patients receiving alendronic acid 5 mg/day from the combined studies were: lumbar spine, 2.4%; femoral neck, 2.2%; and trochanter, 1.6%. Total body BMD was maintained with this dose of alendronic acid. The increases in BMD with alendronic acid 10 mg/day were similar to those with alendronic acid 5 mg/day in all patients except for those post-menopausal women not receiving oestrogen therapy. In these women, the increases (relative to placebo) with alendronic acid 10 mg/day were greater than those with alendronic acid 5 mg/day at the lumbar spine (4.1% vs. 1.6%) and trochanter (2.8% vs. 1.7%), but not at other sites. Alendronic acid was effective regardless of dose or duration of glucocorticoid use.

The majority of patients from these studies who remained on at least 7.5 mg/day of prednisone or equivalent continued into a one-year extension. After two years of treatment, spine BMD increased by 3.7% and 5.0% relative to placebo with alendronic acid 5 and 10 mg/day respectively. Significant increases in BMD (relative to placebo) were also observed at the femoral neck, trochanter, and total body. When the data from the three dosage groups (5 or 10 mg for two years or 2.5 mg for one year followed by 10 mg for one year) was pooled, there was a significant reduction in the incidence of patients with a new vertebral fracture at two years (alendronic acid, 0.7% vs placebo, 6.8%).

Paediatric patients:

Alendronate sodium has been studied in a small number of patients with osteogenesis imperfecta under the age of 18 years. Results are insufficient to support the use of alendronate sodium in paediatric patients with osteogenesis imperfecta.

5.2 Pharmacokinetic properties

Absorption

Relative to an intravenous (IV) reference dose, the oral bioavailability of alendronate in women was 0.7% for doses ranging from 5 to 40 mg when administered after an overnight fast and two hours before a standardised breakfast. Oral bioavailability in men (0.6%) was similar to that in women.

Bioavailability was decreased similarly (by approximately 40%) whether alendronate 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 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 the 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 IV 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 IV 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 IV 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 6 hours following IV 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 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 IV 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

No additional relevant information.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose, Microcrystalline
Maize Starch
Sodium Starch Glycolate (Type A)
Povidone (K- 30)
Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

The tablets are supplied in PVC/Aclar – Aluminium blister pack and HDPE container pack.

Pack size:

PVC/Aclar – Aluminium blister pack: 10,14,20,28,30,50,56,60,84,90,98,100,112,140 and 250 tablets

HDPE container pack: 30,50,100,250 and 1000 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Milpharm Limited
Ares
Odyssey Business park
West End Road
South Ruislip HA4 6QD
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 1050/019/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 7th October 2011

10 DATE OF REVISION OF THE TEXT

July 2012