

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Alendronic Acid Bluefish Once weekly 70 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains the equivalent of 70 mg of alendronic acid as 91.37 mg sodium alendronate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

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

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of postmenopausal osteoporosis. Alendronic Acid Bluefish Once weekly 70 mg tablets reduces the risk of vertebral and hip fractures.

4.2 Posology and method of administration

The recommended dosage is one 70 mg tablet once weekly.

To permit adequate absorption of alendronate:

Alendronic Acid Bluefish Once weekly 70 mg tablets must be taken at least 30 minutes before the first food, beverage, or medicinal product of the day with plain water only. Other beverages (including mineral water), food and some medicinal products are likely to reduce the absorption of alendronate (see 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 Bluefish Once weekly 70 mg tablets 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 Bluefish Once weekly 70 mg tablets 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 Bluefish Once weekly 70 mg tablets.
- Alendronic Acid Bluefish Once weekly 70 mg tablets 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: In clinical studies there was no age-related difference in the efficacy or safety profiles of alendronate. Therefore, no dosage adjustment is necessary for the elderly.

Use in renal impairment: No dosage adjustment is necessary for patients with GFR greater than 35 ml/min. Alendronic Acid Bluefish Once weekly 70 mg tablets is not recommended for patients with renal impairment where GFR is less than 35 ml/min, due to lack of experience.

Paediatric population: 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).

Alendronic Acid Bluefish Once weekly 70 mg tablets have not been investigated in the treatment of glucocorticoid-induced osteoporosis.

Method of administration

Oral use.

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 listed in 6.1.
- Hypocalcaemia
- See also section 4.4.

4.4 Special warnings and precautions for use

Alendronate can cause local irritation of the upper gastro-intestinal mucosa. Because there is a potential for worsening of the underlying disease, caution should be used when alendronate is given to patients with active upper gastro-intestinal problems, such as dysphagia, oesophageal disease, gastritis, duodenitis, ulcers, or with a recent history (within the previous year) of major gastro-intestinal disease such as peptic ulcer, or active gastro-intestinal bleeding, or surgery of the upper gastro-intestinal tract other than pyloroplasty (see section 4.3). In patients with known Barrett's oesophagus, prescribers should consider the benefits and potential risks of alendronate 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 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 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.

The following risk factors should be considered when evaluating an individual's risk of developing osteonecrosis of the jaw:

- potency of the bisphosphonate (highest for zoledronic acid), route of administration (see above) and cumulative dose
- cancer, chemotherapy, radiotherapy, corticosteroids, smoking
- a history of dental disease, poor oral hygiene, periodontal disease, invasive dental procedures and poorly fitting dentures

A dental examination with appropriate preventive dentistry should be considered prior to treatment with oral bisphosphonates in patients with poor dental status.

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.

During bisphosphonate treatment, all patients should be encouraged to maintain good oral hygiene, receive routine dental check-ups, and report any oral symptoms such as dental mobility, pain, or swelling.

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.

A typical 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.

In post-marketing experience, there have been rare reports of severe skin reactions including Stevens Johnson syndrome and toxic epidermal necrolysis.

Patients should be instructed that if they miss a dose of Alendronic Acid Bluefish Once weekly 70 mg tablets, 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 section 4.2).

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

Osteonecrosis of the external auditory canal has been reported with bisphosphonates, mainly in association with long-term therapy. Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma. The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving bisphosphonates who present with ear symptoms including chronic ear infections.

Hypocalcaemia must be corrected before initiating therapy with alendronate (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 Bluefish Once weekly 70 mg tablets.

Due to positive effects of alendronate in increasing bone mineral, decreases in serum calcium and phosphate may occur especially in patients taking glucocorticoids in whom calcium absorption may be decreased. These are usually small and asymptomatic. However, there have been rare 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.

Alendronic Acid Bluefish Once weekly 70 mg tablets

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interactions

If taken at the same time, it is likely that food and beverages (including mineral water), calcium supplements, antacids, and some oral medicinal products will interfere with absorption of alendronate. Therefore, patients must wait at least 30 minutes after taking Alendronate Bluefish 70 mg tablets before taking any other oral medicinal product (see section 4.2 and section 5.2).

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

Pregnancy:

Alendronate 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 section 5.3).

Lactation:

It is not known whether alendronate is excreted into human breast milk. Alendronate should not be used by breast-feeding women.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, certain adverse reactions that have been reported with 'Alendronate Bluefish 70 mg tablets' may affect some patients' ability to drive or operate machinery. Individual responses to 'Alendronate Bluefish 70 mg tablets' may vary (see section 4.8).

4.8 Undesirable effects

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

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

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

	One-Year Study		Three-Year Studies	
	Alendronate Once Weekly 70 mg (n = 519)	Alendronate 10 mg/day (n = 370)	Alendronate 10 mg/day (n = 196)	Placebo (n = 397)
	%	%	%	%
<i>Gastro-intestinal</i>				
abdominal pain	3.7	3.0	6.6	4.8

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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
diarrhoea	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
<i>Musculoskeletal</i>				
musculoskeletal (bone, muscle or joint) pain	2.9	3.2	4.1	2.5
muscle cramp	0.2	1.1	0.0	1.0
<i>Neurological</i>				
headache	0.4	0.3	2.6	1.5

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

- Very common (≥1/10)
- Common (≥ 1/100 to < 1/10)
- Uncommon (≥ 1/1,000 to < 1/100)
- Rare (≥ 1/10,000 to < 1/1,000)
- Very rare (< 1/10,000)

<i>Immune system disorders:</i>	<i>Rare:</i> hypersensitivity reactions including urticaria and angioedema
<i>Metabolism and nutrition disorders:</i>	<i>Rare:</i> symptomatic hypocalcaemia, often in association with predisposing conditions.§
<i>Nervous system disorders:</i>	<i>Common:</i> headache, dizziness† <i>Uncommon:</i> dysgeusia†
<i>Eye disorders:</i>	<i>Uncommon:</i> eye inflammation (uveitis, scleritis, episcleritis)
<i>Ear and labyrinth disorders:</i>	<i>Common:</i> vertigo†
<i>Gastrointestinal disorders</i>	<i>Common:</i> abdominal pain, dyspepsia, constipation, diarrhoea,

	<p>flatulence, oesophageal ulcer*, dysphagia*, abdominal distension, acid regurgitation</p> <p><i>Uncommon:</i> nausea, vomiting, gastritis, oesophagitis*, oesophageal erosions*, melena†</p> <p><i>Rare:</i> oesophageal stricture*, oropharyngeal ulceration*, upper gastrointestinal PUBs (perforation, ulcers, bleeding) §</p>
<p><i>Skin and subcutaneous tissue disorders:</i></p>	<p><i>Common:</i> alopecia†, pruritus†</p> <p><i>Uncommon:</i> rash, erythema</p> <p><i>Rare:</i> rash with photosensitivity, severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis ‡</p>
<p><i>Musculoskeletal and connective tissue disorders:</i></p>	<p><i>Very common:</i> musculoskeletal (bone, muscle or joint) pain which is sometimes severe†§</p> <p><i>Common:</i> joint swelling†</p> <p><i>Rare:</i> Osteonecrosis of the jaw#§; atypical subtrochanteric and diaphyseal femoral fractures</p>

	(bisphosphonate class adverse reaction)^ Very rare: Osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction)
General disorders and administration site conditions:	<i>Common:</i> asthenia [†] , peripheral oedema [†] <i>Uncommon:</i> transient symptoms as in an acute-phase response (myalgia, malaise and rarely, fever), typically in association with initiation of treatment [†] .
<p>§See section 4.4</p> <p>†Frequency in Clinical Trials was similar in the drug and placebo group.</p> <p>*See sections 4.2 and 4.4</p> <p>‡This adverse reaction was identified through post-marketing surveillance. The frequency of rare was estimated based on relevant clinical trials.</p> <p>^Identified in postmarketing experience</p>	

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V*.

4.9 Overdose

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

ATC Code: M05B A04

The active ingredient of Alendronate Bluefish 70 mg tablets, alendronate monosodium trihydrate, is a bisphosphonate that inhibits osteoclastic bone resorption with no direct effect on bone formation. Preclinical studies have shown preferential

localisation of alendronate to sites of active resorption. Activity of osteoclasts is inhibited, but recruitment or attachment of osteoclasts is not affected. The bone formed during treatment with alendronate is of normal quality.

Treatment of post-menopausal osteoporosis

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

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

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

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

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

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

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 $< 8.0\text{mg/dl}$ (2.0mmol/l) and serum phosphate to $\leq 2.0\text{mg/dl}$ (0.65mmol/l) were similar in both treatment groups.

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

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

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

Distribution

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

Biotransformation

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

Elimination

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

Characteristics in patients

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

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Crospovidone
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Al/Al blister

Packs of 2, 4, 8,12, 40 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Bluefish Pharmaceuticals AB
P.O. Box 49013
100 28 Stockholm
Sweden

8 MARKETING AUTHORISATION NUMBER

PA1436/004/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24th April 2009
Date of last renewal: 6th March 2014

10 DATE OF REVISION OF THE TEXT

June 2020