Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Alendromax Once Weekly 70mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 70mg alendronic acid (as sodium alendronate trihydrate)

Excipient:
Each tablet contains 142.64 mg lactose monohydrate

For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.
White to off-white, oval tablet, embossed "AN 70" on one side and the 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.

The recommended dose is one 70 mg tablet per week.

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 Alendromax Once Weekly on an individual patient basis, particularly after 5 or more years of use.

To permit adequate absorption of alendronate:
Alendromax Once Weekly 70mg 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 4.5 'Interaction with other medicinal products and other forms of interaction').

To facilitate delivery to the stomach and thus reduce the potential for local and oesophageal irritation/adverse experiences (see 4.4 'Special warnings and precautions for use'):

- Alendromax Once Weekly 70mg 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 Alendromax Once Weekly 70mg 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 Alendromax Once Weekly 70mg Tablets.
- Alendromax Once Weekly 70mg 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 4.4 ‘Special warnings and precautions for use’).

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. Alendronate is not recommended for patients with renal impairment where GFR is less than 35 ml/min, due to lack of experience.

Use in children (under 18 years): Alendronate has been studied in a small number of patients with osteogenesis imperfecta under 18 years of age. Results are insufficient to support its use in children. Alendromax Once Weekly 70mg Tablets have not been investigated in the treatment of glucocorticoids induced osteoporosis.

4.3 Contraindications

- Abnormalities of the oesophagus and other factors which delay oesophageal emptying such as stricture or achalasia.
- Inability to stand or sit upright for at least 30 minutes.
- Hypersensitivity to alendronate or to any of the excipients.
- Hypocalcaemia.

See also 4.4 Special warnings and precautions for use.

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 gastrointestinal tract other than pyloroplasty (see 4.3 ‘Contraindications’).

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 signalling 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.

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, smoking).

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.

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.

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 Alendromax Once Weekly 70mg 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 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 Alendromax Once Weekly 70mg Tablets.

Due to the 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 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.

Excipients
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

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 30 minutes after taking alendronate before taking any other oral medicinal product (see 4.2 ‘Posology and method of administration’ and 5.2 ‘Pharmacokinetic properties’).

No other interactions with medicinal products of clinical significance are anticipated. A number of patients in the clinical trials received oestrogen (intravaginal, transdermal, or oral) while taking 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
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 5.3 ‘Preclinical safety data’).

Use during 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 Alendromax may affect some patients' ability to drive or operate machinery. Individual responses to Alendromax may vary. (See 4.8 Undesirable effects).

4.8 Undesirable effects

In a one-year study in post-menopausal women with osteoporosis the overall safety profiles of Alendronate sodium 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 ≥1% in either treatment group in the one-year study, or in ≥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	
	'Fosamax' Once Weekly 70 mg (n = 519) %	alendronate 10 mg/day (n = 370) %	alendronate 10 mg/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
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
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 post-marketing 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*, 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, poor oral hygiene and smoking are also deemed as risk factors; severe musculoskeletal (bone, muscle or joint) pain (see 4.4 'Special warnings and precautions for use').

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

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 alendronate 10 mg/day versus approximately 12 and 3% of those taking placebo. However, the incidences of decreases in serum calcium to <8.0 mg/dl (2.0 mmol/l) and serum phosphate to ≤2.0 mg/dl (0.65 mmol/l) were similar in both treatment groups.

4.9 Overdose

Hypocalcaemia, hypophosphataemia and upper 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: Drugs for treatment of bone diseases, bisphosphonates.

ATC code: M05BA04

The active substance in Alendromax Once Weekly 70mg tablets, sodium alendronate 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 therapeutic equivalence of alendronate once-weekly tablets (n=519) and alendronate 10 mg daily (n=370) was demonstrated in a one-year multicentre study in post-menopausal women with osteoporosis. The mean increase from baseline of BMD in the lumbar spine after one year was 5.1 % (95 % confidence interval: 4.8, 5.4 %) in the group receiving 70 mg once per week and 5.4 % (95 % confidence interval: 5.0, 5.8 %) in the group receiving 10 mg daily. The average increases in BMD in the group receiving 70 mg once per week and in the group receiving 10 mg daily were 2.3 % and 2.9 % in the femoral neck and 2.9 % and 3.1 % over the total hip. The two treatment groups were also similar with regard to increased bone density in other parts of the skeleton.

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 body 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 ³1 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 ³1 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 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

3 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/Aluminium) packs containing 2, 4, 8, 12 and 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

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8 MARKETING AUTHORISATION NUMBER

PA 1130/20/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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