Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Alendronic Acid Once Weekly 70 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient with known effect:
Each tablet contains 135,5 mg lactose.

For the 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 "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

Posology
The recommended dose is one 70 mg tablet **once weekly**.

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 alendronate on an individual patient basis, particularly after 5 or more years of use.

Elderly
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.

Renal impairment
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.

Hepatic impairment
No dose adjustment is necessary.

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).

Method of administration
For oral use.

To obtain satisfactory absorption of alendronate

Alendronic Acid Once Weekly 70mg 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 section 4.5).

To assist delivery to the stomach and thus reduce the risk of irritation/side effects locally and in the oesophagus (see section 4.4)

- Alendronic Acid Once Weekly 70mg 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).
- Alendronic Acid Once Weekly Tablets should be swallowed whole. Patients should not crush or chew the tablet or allow the tablet 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 Alendronic Acid Once Weekly 70mg Tablets.
- Alendronic Acid Once Weekly 70mg 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).

Alendronic Acid Once Weekly 70mg Tablets have not been investigated in the treatment of glucocorticoid-induced osteoporosis.

4.3 Contraindications

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- 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
- hypocalcaemia

4.4 Special warnings and precautions for use

Upper gastrointestinal adverse reactions
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). In patients with known Barrett's oesophagus, prescribers should consider the benefits and potential risks of alendronate on an individual patient basis.

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 or perforation, 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). Patients should be informed that the risk of oesophageal problems may increase if they do not follow these instructions.

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

Missed dose

Patients should be instructed that if they miss a dose of Alendronic Acid Once Weekly, they should take one tablet on the morning after they remember. They must 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.

Renal impairment
Alendronate is not recommended for patients with impaired renal function where GFR is less than 35 ml/min (see section 4.2).

Bone and mineral metabolism
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). Other disorders affectingmineral 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.

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 hypocalcaemia, which have occasionally been severe and often occurred in patients with predisposing conditions (e.g. hypoparathyroidism, vitamin D deficiency and calcium malabsorption).
It is particularly important to ensure that patients taking glucocorticoids have an adequate calcium and vitamin D intake.

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.

Osteonecrosis of the jaw
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, angiogenesis inhibitors, 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.

Osteonecrosis of the external auditory canal

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.

Musculoskeletal pain
Bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates. In post-marketing experience, these symptoms have rarely been seen 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 treatment. A subset had recurrence of symptoms when rechallenged with the same medicinal product or another bisphosphonate.

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

Alendronic Acid Once Weekly 70mg tablets contains lactose and sodium.
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.
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 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 sections 4.2 and 5.2).

No other clinically significant alendronate 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.

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

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 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data from the use of alendronate in pregnant women. Studies in animals have shown reproductive toxicity.
Alendronate should not be used in pregnancy. Alendronate given to pregnant rats caused hypocalcaemia-related dystocia (see section 5.3).

Breast-feeding
It is not known whether alendronate/metabolites are excreted into breast milk in humans. A risk to the newborns/infants cannot be excluded.Alendronate should not be used by breast-feeding women.

Fertility
Bisphosphonates are incorporated into the bone matrix, from which they are gradually released over a period of years. The amount of bisphosphonate incorporated into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the dose and duration of bisphosphonate use (see section 5.2). There are no data on foetal risk in humans. However, there is a theoretical risk of foetal harm, predominantly skeletal, if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on the risk has not been studied.

4.7 Effects on ability to drive and use machines

Alendronate has no or negligible direct influence on the ability to drive and use machines.
Certain side effects have been reported during treatment with alendronate which may, in some patients, impair the ability to drive or use machines. The reaction to alendronate may differ from individual to individual (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile
In a one-year study in post-menopausal women with osteoporosis the overall safety profiles for alendronate once-weekly 70 mg tablets (n=519) and alendronate 10 mg daily (n=370) were similar.

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.

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:

	The one-year study	*Three-year studies*		
	Alendronate once-weekly 70 mg (n=519) *%*	*Alendronate 10 mg daily (n=370) %*	*Alendronate 10 mg daily (n=196) %*	*Placebo (n=397) %*
Gastrointestinal				
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 distension	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 pain (bone, muscle or joints)	2.9	3.2	4.1	2.5
Muscle cramps	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:
Frequencies are defined as:
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)

Immune system disorders:
Rare: hypersensitivity reactions including urticaria and angioedema

Metabolism and nutrition disorders:
Rare: symptomatic hypocalcaemia, often in association with predisposing conditions.[§]

Nervous system disorders:

Common: headache, dizziness[†]
Uncommon: dysgeusia[†]

Eye disorders:
Uncommon: eye inflammation (uveitis, scleritis, episcleritis)

Ear and labyrinth disorders:
Common: vertigo[†]
Very rare: Osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction)

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) [§]

Skin and subcutaneous tissue disorders:
Common: alopecia[†], pruritus[†]
Uncommon: rash, erythema
Rare: rash with photosensitivity, severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis[‡]

Musculoskeletal and connective tissue disorders:
Very common: musculoskeletal (bone, muscle or joint) pain which is sometimes severe[†§]
Common: joint swelling[†]
Rare: Osteonecrosis of the jaw[‡§], atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction)

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

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms
Hypocalcaemia, hypophosphataemia and upper gastrointestinal side effects such as upset stomach, heartburn, oesophagitis, gastritis or ulcer can occur on oral overdosage.

Management
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: M05B A04

The active substance in Alendronic Acid 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 ≥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 %).

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.

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

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 the medicinal product 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 medicinal products by those systems in humans.

Renal impairment
Preclinical studies show that the medicinal product 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

Non-clinical data 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 in order to protect from moisture.

6.5 Nature and contents of container

The tablets are packed in a triplex blister: PVC/PE/PVDC/Alu and are inserted in a carton.

Pack sizes:
Blister: 2, 4, 8, 12, 24, 40 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Newtown
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0711/102/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24th July 2006
Date of last authorisation: 3rd December 2009

10 DATE OF REVISION OF THE TEXT

November 2019