AUSTRALIAN PRODUCT INFORMATION

FONAT®

(alendronate sodium) tablet

1 NAME OF THE MEDICINE

Alendronate sodium

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Bisphosphonates are synthetic analogs of pyrophosphate that bind to the hydroxyapatite found in bone. FONAT contains alendronate sodium which is a bisphosphonate that acts as a potent, specific inhibitor of osteoclast-mediated bone resorption.

Each tablet contains 91.37 mg of alendronate sodium as the active ingredient. This is the molar equivalent to 70 mg of alendronic acid.

Excipients with known effect: trace quantities of sulfites and sugars as lactose

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

FONAT 70 mg white bi-convex tablets are debossed "AD70" on one side and "G" on the reverse.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

FONAT is indicated for the treatment of:

- Osteoporosis*, including glucocorticoid-induced osteoporosis.

FONAT is indicated for the prevention of:

- Glucocorticoid-induced osteoporosis in those patients on long term corticosteroid therapy (Section 5.1 PHARMACODYNAMIC PROPERTIES - CLINICAL TRIALS - Glucocorticoid – Induced Osteoporosis)

*Prior to treatment, osteoporosis must be confirmed by:

- the finding of low bone mass of at least 2 standard deviations below the mean for young adults (gender specific), or by
- the presence of osteoporotic fracture.

4.2 DOSE AND METHOD OF ADMINISTRATION

Alendronate must be taken at least 30 minutes before the first food, beverage or medication of the day with plain water only. Other beverages (including mineral water), food and some medications are likely to reduce the absorption of alendronate (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

FONAT should only be taken upon rising for the day. To facilitate delivery to the stomach and thus reduce the potential for oesophageal irritation, alendronate should only be swallowed upon arising for the day with a full glass of water and patients should not lie down for at least 30 minutes and until after their first food of the day. Alendronate should not be taken at bedtime or before arising for the day. Failure to follow these instructions may increase the risk of oesophageal adverse experiences (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Severe oesophageal ulceration has been reported in patients taking alendronate (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Patients should be instructed that if they develop symptoms of oesophageal disease (such as difficulty or pain upon swallowing, retrosternal pain or new or worsening heartburn) they should stop taking alendronate and consult their doctor.

In clinical trials, alendronate was administered with appropriate calcium and vitamin D supplementation. The use of vitamin D as the sole treatment of osteoporosis has not been established.

Patients should receive supplemental calcium and/or vitamin D if dietary intake is inadequate (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Physicians should consider the vitamin D intake from vitamins and dietary supplements. However, these supplements should not be taken at the same time as FONAT (see above).

No dosage adjustment is necessary for the elderly or patients with mild to moderate renal insufficiency (creatinine clearance 35 to 60 mL/minute). Alendronate is not recommended for patients with more severe renal insufficiency (creatinine clearance < 35 mL/minute).

Although no specific studies have been conducted on the effects of switching patients on another therapy for osteoporosis to FONAT, there are no known or theoretical safety concerns related to alendronate in patients who previously received any other antiosteoporotic or antipagetic therapy.

Treatment of osteoporosis

The recommended dosage is one FONAT (70 mg) tablet once weekly.

Treatment and prevention of glucocorticoid – induced osteoporosis

The recommended dosage in selected patients is one 5 mg tablet of alendronate once a day, except for post-menopausal women not receiving estrogen, for whom the recommended dosage is one 10 mg tablet of alendronate once per day (see Section 5.1 PHARMACODYNAMIC PROPERTIES - CLINICAL TRIALS - Glucocorticoid – Induced Osteoporosis).

The optimal duration of use has not been determined. All patients on bisphosphonate therapy should have the need for continued therapy re-evaluated on a periodic basis (see Section 5.1 PHARMACODYNAMIC PROPERTIES - CLINICAL TRIALS).

4.3 CONTRAINDICATIONS

Abnormalities of the oesophagus which delay oesophageal emptying, such as stricture or achalasia.

Inability to stand or sit upright for at least 30 minutes.

Hypersensitivity to any component of this product.

Hypocalcaemia (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Severe oesophageal ulceration has been reported in patients taking alendronate (see Section 4.2 - DOSE AND METHOD OF ADMINISTRATION). Doctors should therefore be alert to any signs or symptoms signalling a possible oesophageal reaction. Patients should be instructed to discontinue FONAT and seek medical attention if they develop dysphagia, odynophagia or retrosternal pain.

General

Causes of osteoporosis other than hypogonadism, ageing and glucocorticoid use should be considered.

If there are clinical reasons to suspect hypocalcaemia and/or vitamin D deficiency (serum levels 25 hydroxyvitamin D < 9 nmol/L), the appropriate diagnostic tests should be performed. Hypocalcaemia must be corrected before initiating therapy with alendronate (see Section 4.3 CONTRAINDICATIONS). Other

disturbances of mineral metabolism, e.g. vitamin D deficiency, should also be effectively treated. In patients with these conditions, serum calcium and symptoms of hypocalcaemia should be monitored during therapy with alendronate.

Small, asymptomatic decreases in serum calcium and phosphate may occur, especially in patients with Paget's disease, in whom the pretreatment rate of bone turnover may be greatly elevated, and in patients receiving glucocorticoids, in whom calcium absorption may be decreased.

Ensuring adequate calcium and vitamin D intake is especially important in patients with Paget's disease of bone and in patients receiving glucocorticoids.

Alendronate, like other bisphosphonates, may cause local irritation of the upper gastrointestinal mucosa.

Oesophageal adverse experiences such as oesophagitis, oesophageal ulcers and oesophageal erosions, rarely followed by oesophageal stricture or perforation, have been reported in patients receiving treatment with alendronate. In some cases these have been severe and required hospitalisation.

The risk of severe oesophageal adverse experiences appears to be greater in patients who lie down after taking alendronate and/or who fail to swallow the dose with a full glass of water, and/or who continue to take alendronate after developing symptoms suggestive of oesophageal irritation. Therefore, it is very important that the full dosing instructions are provided to, and understood by, the patient (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

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.

Because of possible irritant effects of alendronate on the upper gastrointestinal mucosa and a potential for worsening of the underlying disease, caution should be used when alendronate is given to patients with active upper gastrointestinal problems such as dysphagia, oesophageal diseases (including known Barrett's oesophagus), gastritis, duodenitis or ulcers.

Dental

Localised osteonecrosis of the jaw (ONJ), which is generally associated with tooth extraction and/or local infection (including osteomyelitis) with delayed healing, has been reported rarely with oral bisphosphonates including FONAT (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) - POST-MARKETING EXPERIENCE). As of May 2004, ONJ after bisphosphonate treatment has been described in a total of 99 cases in two large case series, 7 of which were taking oral bisphosphonates. As of 3 November 2006, the Australian Adverse Drug Reactions Advisory Committee has received 25 reports of ONJ in patients receiving alendronate. Most reported cases of bisphosphonate-associated ONJ have been in cancer patients treated with intravenous bisphosphonates. Known risk factors for ONJ include a diagnosis of cancer, concomitant therapies (e.g. chemotherapy, radiotherapy, corticosteroids, angiogenesis inhibitors), poor oral hygiene, co-morbid disorders (e.g. periodontal and/or other pre-existing dental disease, anaemia, coagulopathy, infection) and smoking.

Prior to treatment with bisphosphonates, a dental examination with appropriate preventative dentistry should be considered in patients with possible risk factors.

Before commencing invasive dental procedures, patients and their dentist should be advised of the risks and reports of ONJ so that dental symptoms, including toothache that develops during treatment can be fully assessed for cause before treatment of the tooth commences.

For patients requiring invasive dental surgery (e.g. tooth extraction, dental implants), there is no definitive data available to establish whether discontinuation of bisphosphonate treatment reduces the risk of ONJ. Therefore, clinical judgement of the treating physician and/or oral surgeon should guide the management plan, including discontinuation of bisphosphonate therapy, of each patient based on individual benefit/risk assessment.

In patients who develop ONJ while on bisphosphonate therapy, the clinical judgement of the treating physician should guide the management plan to include appropriate care by an oral surgeon and discontinuation of bisphosphonate therapy should be based on individual benefit/risk assessment. Surgery at the affected area may exacerbate the condition.

Atypical Stress Fracture

A small number of long-term, usually longer than three years, alendronate-treated patients developed stress fractures of the proximal femoral shaft, also known as insufficiency fractures, some of which occurred in the absence of apparent trauma. Some patients experienced prodromal pain in the affected area, often associated with imaging features of stress fracture, weeks to months before a complete fracture occurred. Approximately one third of these fractures were bilateral; therefore the contralateral femur should be examined in patients who have sustained a femoral shaft stress fracture. The number of reported cases of this condition is very low (some 40 reported cases world-wide in connection with alendronate as of 2008). Patients with suspected stress fractures should be evaluated, including evaluation for known causes and risk factors, e.g., vitamin D deficiency, malabsorption, glucocorticoid use, previous stress fracture, lower extremity arthritis or fracture, extreme or increased exercise, diabetes mellitus, chronic alcohol abuse, and receive appropriate orthopaedic care. Discontinuation of bisphosphonate therapy in patients with stress fractures is advisable pending evaluation of the patient, based on individual benefit/risk assessment. A cause-and-effect relationship between bisphosphonate use and stress fractures has not been excluded.

Musculoskeletal Pain

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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) - POST-MARKETING EXPERIENCE). The time of onset of symptoms varied from one day to several months after starting treatment. Most patients had relief of symptoms after ceasing treatment. A subset experienced a recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.

Use in Renal Impairment

FONAT is not recommended for patients with creatinine clearance less than 35 mL/minute (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Dosing Instructions for Patients

To facilitate delivery to the stomach and thus reduce the potential for oesophageal irritation, patients should be instructed to swallow alendronate with a full glass of water and not to lie down for at least 30 minutes and until after their first food of the day. Patients should not chew or suck on the tablet because of a potential for oropharyngeal ulceration. Patients should be specifically instructed not to take alendronate at bedtime or before rising for the day. Patients should be informed that failure to follow these instructions may increase their risk of oesophageal problems. Patients should be instructed that if they develop symptoms of oesophageal disease, e.g. difficulty or pain upon swallowing, retrosternal pain or new or worsening heartburn, they should stop taking alendronate and consult their doctor.

Patients should be instructed that if they miss a dose of FONAT, 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.

Use in the Elderly

In controlled trials, there was no age-related difference in the efficacy or safety profiles of alendronate.

Paediatric Use

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

Effects on Laboratory Tests

In double-blind, multicentre controlled studies, asymptomatic, mild and transient decreases in serum calcium and phosphate were observed in approximately 18 and 10%, respectively, of patients taking alendronate versus approximately 12 and 3% of those taking placebo. However, the incidences of decreases in serum calcium to < 8.0 mg/dL (2.0 mm) and serum phosphate to ≤ 2.0 mg P/dL (0.65 mm) were similar in both treatment groups.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

If taken at the same time, it is likely that calcium supplements, antacids and other oral medications will interfere with the absorption of alendronate. Therefore, patients must wait at least one-half hour after taking alendronate before taking any other oral medication.

No other drug interactions of clinical significance are anticipated although the concomitant medication with two or more bisphosphonates cannot be recommended because of the lack of clinical data.

Concomitant use of HRT (estrogen +/- progestin) and alendronate was assessed in two clinical studies of one- or two-years duration in postmenopausal osteoporotic women. Combined use of alendronate and HRT resulted in greater increases in bone mass, together with greater decreases in bone turnover, than seen with either treatment alone. In these studies, the safety and tolerability profile of the combination was consistent with those of the individual treatments (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) - CLINICAL STUDIES - Concomitant use with estrogen/ hormone replacement therapy).

Specific interaction studies were not performed. Alendronate (10 mg and 5 mg/day) was used in studies of treatment and prevention of osteoporosis in postmenopausal women, men and glucocorticoid users, with a wide range of commonly prescribed drugs without evidence of clinical adverse interactions. In clinical studies, the incidence of upper gastrointestinal adverse events was increased in patients receiving daily therapy with dosages of alendronate greater than 10 mg and aspirin-containing products. However, this was not observed in studies with alendronate once weekly 70 mg.

Since Non-Steroidal Anti-inflammatory Drug (NSAID) use is associated with gastrointestinal irritation, caution should be used during concomitant use with alendronate.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Respective oral alendronate doses of up to 9 and 15 mg/kg/day had no effect on fertility in male and female rats.

Use in Pregnancy

Pregnancy Category: B3

Alendronate has not been studied in pregnant women and should not be given to them. In studies with pregnant rats, oral doses of alendronate 2 mg/kg/day and above resulted in dystocia due to maternal hypocalcaemia. Fetal weight was reduced in rats at maternal doses greater than 5 mg/kg/day. No teratogenic effects were seen in rats or rabbits at oral doses up to 25 and 35 mg/kg/day respectively.

Use in Lactation

Alendronate has not been studied in breastfeeding women and should not be given to them.

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 e.g. dizziness and vertigo that have been reported with alendronate may affect some patients'

ability to drive or operate machinery. Individual responses to alendronate may vary (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical studies

In clinical studies alendronate was generally well tolerated. In studies up to five years in duration, side effects, which usually were mild, generally did not require discontinuation of therapy.

Treatment of osteoporosis

Postmenopausal women

Alendronate has been evaluated for safety in clinical studies in approximately 5,000 postmenopausal patients. In two three-year, placebo-controlled, double-blind multicentre studies, discontinuation of therapy due to any clinical adverse experience occurred in 4.1% of 196 patients treated with alendronate 10 mg/day and 6.0% of 397 patients treated with placebo. Adverse experiences reported by the investigators as possibly, probably or definitely drug related in greater than or equal to 1% of patients treated with either alendronate 10 mg/day or placebo are presented in Table 1.

Table 1: Drug related adverse experiences reported in ≥ 1% of patients

Adverse experience	**Alendronate 10 mg/day (%) (n=196)**	**Placebo (%) (n=397)**
Gastrointestinal		
Abdominal pain	6.6	4.8
Nausea	3.6	4.0
Dyspepsia	3.6	3.5
Diarrhoea	3.1	1.8
Constipation	3.1	1.8
Flatulence	2.6	0.5
Acid regurgitation	2.0	4.3
Oesophageal ulcer	1.5	0.0
Vomiting	1.0	1.5
Dysphagia	1.0	0.0
Abdominal distention	1.0	0.8
Gastritis	0.5	1.3
Musculoskeletal		
Musculoskeletal pain (bone, muscle or joint)	4.1	2.5
Muscle cramp	0.0	1.0
Nervous system/psychiatric		
Headache	2.6	1.5

Adverse experience	Alendronate 10 mg/day (%) (n=196)	Placebo (%) (n=397)
Dizziness	0.0	1.0
Special senses		
Taste perversion	0.5	1.0

Rarely, rash and erythema have occurred.

In the two-year extension (treatment years 4 and 5) of the above studies, the overall safety profile of alendronate 10 mg/day was similar to that observed during the three-year placebo-controlled period. Additionally, the proportion of patients who discontinued alendronate 10 mg/day due to any clinical adverse experience was similar to that during the first three years of the study.

In the Fracture Intervention Trial, discontinuation of therapy due to any clinical adverse experience occurred in 9.1% of 3,236 patients treated with alendronate 5 mg/day for two years and 10 mg/day for either one or two additional years and 10.1% of 3,223 patients treated with placebo. Discontinuations due to upper gastrointestinal adverse experiences were: alendronate 3.2%; placebo 2.7%. The overall adverse experience profile was similar to that seen in other studies with alendronate 5 or 10 mg/day.

In a one-year, double-blind, multicentre study, the overall safety and tolerability profiles of alendronate 70 mg (once weekly) (n = 519) and alendronate 10 mg daily (n = 370) were similar. Adverse experiences reported by the investigators as possibly, probably or definitely drug related in greater than or equal to 1% of patients treated with either patient group are presented in Table 2.

Table 2: Drug related adverse experiences reported in ≥1% of patients

Adverse experience	Alendronate once weekly 70 mg (%) (n=519)	Alendronate 10mg/day (%) (n=370)
Gastrointestinal		
Abdominal pain	3.7	3.0
Dyspepsia	2.7	2.2
Acid regurgitation	1.9	2.4
Nausea	1.9	2.4
Abdominal distension	1.0	1.4
Constipation	0.8	1.6
Flatulence	0.4	1.6
Gastritis	0.2	1.1
Gastric ulcer	0.0	1.1
Musculoskeletal		
Musculoskeletal pain (bone, muscle or joint)	2.9	3.2
Muscle cramp	0.2	1.1

Concomitant use with estrogen/ hormone replacement therapy

In two studies (of one- and two-years duration) of postmenopausal osteoporotic women (total n = 853), the safety and tolerability profile of combined treatment with alendronate 10 mg once daily and estrogen +/- progestin (n = 354) was consistent with those of the individual treatments.

Men

In a two-year, placebo-controlled, double-blind, multicentre study, the safety profile of alendronate 10 mg daily in 146 men was generally similar to that seen in postmenopausal women.

Other studies in men and women

In a ten-week endoscopy study in men and women (n = 277; mean age 55 years) no difference was seen in upper gastrointestinal tract lesions between alendronate 70 mg (once weekly) and placebo.

In an additional one-year study in men and women (n = 335; mean age 50 years) the overall safety and tolerability profiles of alendronate 70 mg (once weekly) were similar to that of placebo and no difference was seen between men and women.

Treatment and Prevention of glucocorticoid-induced osteoporosis

In two, one-year, placebo-controlled, double-blind, multicentre studies in patients receiving glucocorticoid treatment, the overall safety and tolerability profiles of alendronate 5 and 10 mg/day were generally similar to that of the placebo. Adverse experiences reported by the investigators as possible, probably or definitely drug related in equal or more than 1% of patients treated with either alendronate 5mg/day, 10mg/day or placebo are presented in Table 3.

Table 3: Drug related adverse experiences reported in ≥ 1% of patients

	Alendronate 10 mg/day %	Alendronate 5 mg/day %	Placebo %
Gastrointestinal			
Abdominal pain	3.2	1.9	0.0
Acid regurgitation	2.5	1.9	1.3
Constipation	1.3	0.6	0.0
Melaena	1.3	0.0	0.0
Nausea	0.6	1.2	0.6

Post-marketing experience

The following adverse effects have been reported in post-marketing use with alendronate:

Body as a whole

Hypersensitivity reactions including urticaria and, rarely, angioedema. Transient symptoms as in an acute phase response (myalgia, malaise, asthenia and, rarely, fever) have been reported with alendronate, typically in association with initiation of treatment. Rarely, symptomatic hypocalcaemia has occurred, generally in association with predisposing conditions. Rarely, peripheral oedema.

Gastrointestinal

Nausea, vomiting, oesophagitis, oesophageal erosions, oesophageal ulcers, rarely oesophageal stricture or perforation, and oropharyngeal ulceration and/or stomatitis; rarely, gastric or duodenal ulcers, some severe and with complications (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Localised osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection, including osteomyelitis, often with delayed healing, has been reported rarely (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Skin

Rash (occasionally with photosensitivity), alopecia, pruritus, rarely severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis.

Special senses

Rarely uveitis, scleritis or episcleritis. Cholesteatoma of the external auditory canal (focal osteonecrosis) has been reported rarely.

Musculoskeletal

Bone, joint, and/or muscle pain, rarely severe and/or incapacitating (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE); joint swelling, atypical stress fracture (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Nervous system

Dizziness, vertigo, dysgeusia.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Symptoms

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

Treatment

No specific information is available on the treatment of alendronate overdosage. Administration of milk or antacids to bind alendronate should be considered.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Alendronate is a bisphosphonate that, in animal studies, localises preferentially to sites of bone resorption, specifically under osteoclasts, and inhibits osteoclastic bone resorption with no direct effect on bone formation. Since bone formation and bone resorption are coupled, bone formation is also reduced, but less so than resorption, leading to progressive gains in bone mass (see Section 5.1 PHARMACODYNAMIC PROPERTIES - CLINICAL TRIALS). Following exposure to alendronate, normal bone is formed that incorporates alendronate into its matrix where it is pharmacologically inactive.

The relative inhibitory activities on bone resorption and mineralisation of alendronate and etidronate were compared in growing rats. The lowest dose of alendronate that interfered with bone mineralisation (leading to osteomalacia) was 6000-fold the antiresorptive dose. The corresponding safety margin for etidronate was one

to one. These data indicate that, unlike etidronate, alendronate administered in therapeutic doses is highly unlikely to induce osteomalacia.

Osteoporosis

WHO utilises the definition of osteoporosis as a disease characterised by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk. The diagnosis may be confirmed by the finding of low bone mass (for example, at least 2 standard deviations below the gender specific mean for young adults) or by the presence or history of osteoporotic fracture. It occurs in both males and females but is most common among women following menopause, when bone turnover increases and the rate of bone resorption exceeds that of bone formation, leading to loss of bone mass.

Osteoporosis in postmenopausal women

Daily oral doses of alendronate in postmenopausal women produced biochemical changes indicative of dose-dependent inhibition of bone resorption, including decreases in urinary calcium and urinary markers of bone collagen degradation (such as hydroxyproline, deoxypyridinoline, and cross-linked N-telopeptides of type I collagen). These biochemical changes returned toward baseline values as early as three weeks following the discontinuation of alendronate despite the long retention of alendronate in the skeleton.

Long-term treatment of osteoporosis with alendronate 10 mg/day (for up to five years) reduced urinary excretion of markers of bone resorption, deoxypyridinoline and cross-linked N-telopeptides of type I collagen, by approximately 50% and 70%, respectively, to reach levels similar to those seen in healthy pre-menopausal women. Similar decreases were seen in patients in osteoporosis prevention studies who received alendronate 5 mg/day. The decrease in the rate of bone resorption indicated by these markers was evident as early as one month and at three to six months reached a plateau that was maintained for the entire duration of treatment with alendronate. In osteoporosis treatment studies alendronate 10 mg/day decreased the markers of bone formation, osteocalcin and total serum alkaline phosphatase, by approximately 50% and 25-30%, respectively, to reach a plateau after 6 to 12 months. Similar though slightly lower reductions in the rate of bone turnover were observed in postmenopausal women during one-year studies with alendronate 70 mg (once weekly) for the treatment of osteoporosis. In osteoporosis prevention studies alendronate 5 mg/day decreased these markers by approximately 40% and 15%, respectively.

Osteoporosis in men

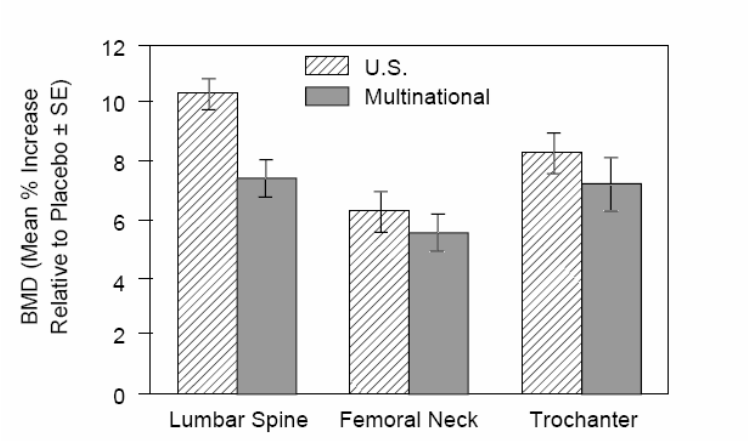
Even though osteoporosis is less prevalent in men than in postmenopausal women, a significant proportion of osteoporotic fractures occur in men. The prevalence of vertebral deformities appears to be similar in men and women. All men with osteoporosis should be investigated for hypogonadism and, if necessary, treated for this condition. Treatment of men with osteoporosis with alendronate 10 mg/day for two years reduced urinary excretion of cross-linked N-telopeptides of type I collagen by approximately 60% and bone-specific alkaline phosphatase by approximately 40%. Similar reductions in cross-linked N-telopeptides of type I collagen were seen in men receiving alendronate 70 mg (once weekly).

Clinical Trials

Effect on bone mineral density

The efficacy of alendronate 10 mg once daily in postmenopausal women with osteoporosis was demonstrated in two large three year multicentre studies of virtually identical design, one performed in the United States and the other in 15 different countries (Multinational), which enrolled 478 and 516 patients, respectively. Figure 1 shows the mean increases in bone mineral density (BMD) of the lumbar spine, femoral neck and trochanter in patients receiving alendronate 10 mg/day relative to placebo-treated patients at three years for each of these studies.

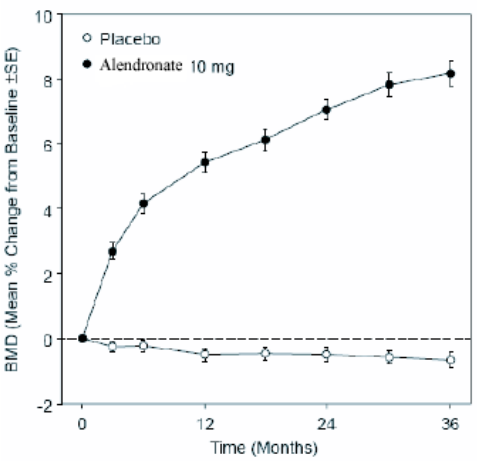
Figure 1: Increase in bone density (BMD) in two studies at three years*



* Dose = 10mg alendronate sodium/day

These increases were highly significant relative both to baseline and placebo at each measurement site in each study. Increases in BMD were evident as early as three months and continued throughout the entire three years of treatment. See Figure 2 for lumbar spine results. In the two year extension of these studies, treatment with alendronate 10 mg/day resulted in continued increases in BMD at the lumbar spine and trochanter (absolute additional increases between years 3 and 5: lumbar spine 0.94%; trochanter 0.88%). BMD at the femoral neck, forearm and total body were maintained. Thus, alendronate appears to reverse the progression of osteoporosis as assessed by increased bone mineral density. Alendronate was similarly effective regardless of age, race, baseline rate of bone turnover, renal function and use of concomitant medications.

Figure 2: Time course of effect of alendronate versus placebo: %change in lumbar spine bone mineral density (BMD) from baseline



In patients with postmenopausal osteoporosis treated with alendronate 10 mg/day for one or two years the effects of treatment withdrawal were assessed. Following discontinuation, there were no further increases in bone mass and the rates of bone loss were similar to those in the placebo groups. These data indicate that continuous treatment with alendronate is required to produce progressive increases in bone mass.

The therapeutic equivalence of alendronate 70 mg (once weekly) (n = 519) and alendronate 10 mg daily (n = 370) was demonstrated in a one-year, double-blind, multicentre study of postmenopausal women with osteoporosis. The mean increases from baseline in lumbar spine BMD at one year were 5.1% (4.8, 5.4%; 95% CI) in the 70 mg once weekly group and 5.4% (5.0, 5.8%; 95% CI) in the 10 mg daily group. The two treatment groups were also similar with regard to BMD increases at other skeletal sites. While there are no placebo-controlled fracture data for the alendronate 70 mg (once weekly) tablet, the increases in bone density support

the expectation that alendronate 70 mg (once weekly) will have effects to reduce the incidence of fractures similar to those of the 10 mg daily treatment (see below). The study was not designed to evaluate the relative compliance of alendronate 70 mg (once weekly) and 10 mg daily.

Effect on fracture incidence

Although the US and multinational studies (see above) were not designed to assess fracture rates as the primary endpoint, preplanned analysis of the data pooled across once daily doses at three years revealed a statistically significant and clinically meaningful 48% reduction in the proportion of patients treated with alendronate experiencing one or more vertebral fractures (3.2%) relative to those treated with placebo (6.2%). Furthermore, of patients who sustained any vertebral fracture, those treated with alendronate experienced less height loss (5.9 mm versus 23.3 mm) due to a reduction in both the number and severity of fractures.

The Fracture Intervention Trial (FIT) consisted of two studies in postmenopausal women: the three-year study of patients who had at least one baseline vertebral (compression) fracture and the four year study of patients with low bone mass but without baseline vertebral fracture.

Fracture Intervention Trial: three-year study (patients with at least one baseline vertebral fracture)

This randomised, double-blind, placebo-controlled 2,027 patient study, (alendronate n = 1,022; placebo n = 1,005) demonstrated that treatment with alendronate resulted in clinically significant reductions in fracture incidence at three years as shown in Table 4. Data also showed statistically significant reductions in painful vertebral fractures and clinical fractures at other sites. Similar reductions of hip and wrist fractures were seen in five pooled osteoporosis treatment studies of two- or three-years duration.

Table 4: Effect of alendronate on fracture incidence in the three-year study of FIT (% of patients with vertebral fracture at baseline)

Patients with	Alendronate (n=1022)	Placebo (n=1005)	Absolute reduction in fracture incidence	Relative reduction (%) in fracture risk	P value
≥ 1 new vertebral fracture	7.9	15.0	7.1	47	< 0.001*
≥ 2 new vertebral fractures	0.5	4.9	4.4	90	< 0.001*
≥ 1 painful vertebral fracture	2.3	5.0	2.7	54	< 0.002†
Any painful (including vertebral) fracture	13.8	18.1	4.3	26	0.007†
HIP fractures	1.1	2.2	1.1	51	0.047†
Wrist (forearm) fractures	2.2	4.1	1.9	48	0.013†
*Mantel-Haenzel chi2 † Log rank test					

Furthermore, in this population of patients with baseline vertebral fracture, treatment with alendronate significantly reduced the incidence of hospitalisations resulting from any cause (25.0% versus 30.7%, a 20% relative risk reduction). This difference appears to be related, at least in part, to the reduction in fracture incidence.

Fracture Intervention Trial: four-year study (patients with low bone mass but without a baseline vertebral fracture)

This randomised, double-blind, placebo-controlled, 4,432 patient study (alendronate, n = 2,214; placebo, n = 2,218) further demonstrated the reduction in fracture incidence due to alendronate. The intent of the study was to recruit women with osteoporosis, i.e. with a baseline femoral neck BMD at least two standard deviations

below the mean for young adult women. However, due to subsequent revisions to the normative values for femoral neck BMD, 31% of patients were found not to meet this entry criterion and thus this study included both osteoporotic and non-osteoporotic women. The results are shown in Table 5 for the patients with osteoporosis.

Table 5: Effect of alendronate on fracture incidence in osteoporotic+ patients in the four-year study of FIT (patients without vertebral fracture at baseline) (% of patients)

Patients with	Alendronate (n=1545)	Placebo (n=1521)	Absolute reduction in fracture incidence	Relative reduction (%) in fracture risk
≥ 1 painful fracture	12.9	16.2	3.3	22†
≥ 1 vertebral fracture++	2.5	4.8	2.3	48‡
≥ 1 painful vertebral fracture	1.0	1.6	0.6	(NS)
HIP fractures	1.0	1.4	0.4	(NS)
Wrist (forearm) fractures	3.6	3.8	-0.1	none

+ Baseline femoral neck BMD at least 2 SD below the mean for young adult women
++ Number evaluable for vertebral fracture: Alendronate, n=1426; placebo, n=1428
ns Not significant. This study was not powered to detect differences at these sites
† p=0.01
‡ p < 0.001

Consistency of fracture results

The reductions in the incidence of vertebral fractures (alendronate versus placebo) in the three- and four-year studies of FIT were consistent with that in the combined US and multinational (US/Mult) treatment studies (see above), in which 80% of the women did not have a vertebral fracture at baseline. During these studies, treatment with alendronate reduced the proportion of women experiencing at least one new vertebral fracture by approximately 50% (three-year FIT: 47% reduction, $p < 0.001$; four-year FIT: 44% reduction, $p = 0.001$ US/Mult, 48% reduction, $p = 0.034$). In addition, alendronate reduced the proportion of women experiencing multiple (two or more) new vertebral fractures by approximately 90% in the US/Mult and three-year FIT studies ($p < 0.001$). Thus, alendronate reduced the incidence of vertebral fractures whether or not patients had experienced a previous vertebral fracture.

Overall, these results demonstrate the consistent efficacy of alendronate in reducing the incidence of fractures, including those of the spine and hip, which are the sites of osteoporotic fracture associated with greatest morbidity.

Bone histology

Bone histology in 270 postmenopausal patients with osteoporosis treated with alendronate at doses ranging from 1 to 20 mg/day for one, two or three years revealed normal mineralisation and structure, as well as the expected decrease in bone turnover relative to placebo. These data, together with the normal bone histology and increased bone strength observed in ovariectomised rats and baboons exposed to long-term alendronate treatment, indicate that bone formed during therapy with alendronate is of normal quality.

Concomitant use with estrogen/hormone replacement therapy

The effects on BMD of treatment with alendronate 10 mg once daily and conjugated estrogen (0.625 mg/day) either alone or in combination were assessed in a two-year, double-blind, placebo-controlled study of hysterectomised postmenopausal osteoporotic women (n = 425). At two years, the increases in lumbar spine BMD from baseline were significantly greater with the combination (8.3%) than with either estrogen or alendronate alone (both 6.0%).

The effects on BMD when alendronate was added to stable doses (for at least one year) of HRT (estrogen +/- progestin) were assessed in a one-year, double-blind, placebo-controlled study in postmenopausal osteoporotic women (n = 428). The addition of alendronate 10 mg once daily to HRT produced, at one year, significantly greater increases in lumbar spine BMD (3.7%) versus 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.

Men

The efficacy of alendronate 10 mg once daily in men with osteoporosis was demonstrated in a two-year, double-blind, placebo-controlled, multicentre study, which enrolled 241 osteoporotic men between the ages of 31 and 87 years. All patients in the study (97.5% of whom were Caucasian) had either: 1) a BMD T score $\leq$ -2 at the femoral neck and $\leq$ -1 at the lumbar spine or 2) a baseline osteoporotic fracture and a BMD T score $\leq$ -1 at the femoral neck. At two years the mean increases relative to placebo in BMD in men receiving alendronate 10 mg daily were: lumbar spine 5.3%; femoral neck 2.6%; trochanter 3.1%; and total body 1.6% (all $p \leq 0.001$). Alendronate was effective regardless of age, gonadal function, baseline rate of bone turnover, or baseline BMD. Consistent with the much larger studies in postmenopausal women, in these men alendronate 10 mg daily reduced the incidence of new vertebral fracture (post hoc analysis; assessment by quantitative radiography) relative to placebo (0.8 versus 7.1%, respectively; $p = 0.017$) and, correspondingly, also reduced height loss (-0.6 versus -2.4 mm, respectively; $p = 0.022$).

The effects of discontinuation of alendronate treatment have not been studied in this population.

Glucocorticoid – Induced Osteoporosis

Sustained use of glucocorticoids is commonly associated with development of osteoporosis and resulting fractures (especially vertebral, hip and rib). It occurs in both males and females of all ages. Bone loss occurs as a result of a lower rate of bone formation relative to that of bone resorption. Alendronate decreases bone resorption without directly inhibiting bone formation.

In clinical studies of one year's duration, alendronate 5 and 10 mg/day reduced cross-linked N-telopeptides of type 1 collagen (a marker of bone resorption) by approximately 60% and reduced bone-specific alkaline phosphatase and total serum alkaline phosphatase (markers of bone formation) by approximately 25 to 30% and 12 to 15%, respectively. As a result of inhibition of bone resorption, alendronate 5 and 10 mg/day induced asymptomatic decreases in serum calcium (approximately 1%) and serum phosphate (approximately 2 to 7%).

The efficacy of alendronate 5 and 10 mg once daily in men and women receiving glucocorticoids (at least 7.5 mg/day of prednisone or equivalent) was demonstrated in two, one-year placebo-controlled, double-blind, multicentre studies (n: total = 560, males = 176) of virtually identical design. Most of the patients were ambulant, Caucasian and non-smokers. The study population included patients with rheumatoid arthritis, polymyalgia rheumatica, systemic lupus erythematosus, pemphigus, asthma, myositis, inflammatory bowel disease, giant cell arteritis, sarcoidosis, myasthenia gravis, chronic obstructive pulmonary disease and nephrotic syndrome. The range and duration of prior corticosteroid use in the studies was 0 to 538 months with a mean of 43.6 months and a median of 12 months. The range of prednisone dose at study commencement was 5 to 135 mg/day with a mean of 18.4 mg and a median of 10 mg daily. Fifty-seven percent of patients had osteopenia/osteoporosis at study commencement. Patients received supplemental calcium and vitamin D. At one year, the mean increases relative to placebo in BMD in patients receiving alendronate 5 mg/day from the combined studies were: lumbar spine, 2.41%; femoral neck, 2.19%; and trochanter, 1.65%. These increases were significant at each site. Total body BMD was maintained with alendronate 5 mg/day indicating that the increase in bone mass of the spine and hip did not occur at the expense of other sites. The increases in BMD with alendronate 10 mg/day were similar to those with alendronate 5 mg/day in all patients except for post-menopausal women not receiving estrogen therapy. In these women, the increases (relative to placebo) with alendronate 10 mg/day were greater than those with alendronate 5 mg/day at the lumbar spine (4.11% vs. 1.56%) and trochanter (2.84% vs. 1.67%), but not at other sites. Alendronate was effective regardless of dose or duration of glucocorticoid use. In addition, alendronate was similarly effective regardless of age (<65 vs. ≥65 years), race (Caucasian vs. other races), gender, baseline BMD, baseline bone turnover, and use with a variety of common medications.

Bone histology was normal in the 49 patients biopsied at the end of one year who received alendronate at doses of up to 10 mg/day.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Relative to an intravenous reference dose, the mean oral 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. There was substantial variability both within and between patients, coefficient of variation 63 and 77% respectively. 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 30 minutes before a standardised breakfast. In osteoporosis, 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 normal subjects, oral prednisone (20 mg three times daily for five days) did not substantially alter the oral bioavailability of alendronate (alendronate alone: 0.73%; alendronate plus prednisone: 0.87%).

Distribution

Preclinical studies show that alendronate transiently distributes to soft tissues following 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 L in humans. Concentrations of alendronate in plasma following therapeutic oral doses are generally below the limits of quantification (<5 nanogram/mL). Protein binding in human plasma is approximately 78%.

Metabolism

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

Excretion

Following a single 10 mg 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; the renal clearance of alendronate was 71 mL/min. Plasma concentrations fell by more than 95% within 6 hours following IV administration, due to distribution to the bone and excretion in the urine. The terminal half-life in humans is estimated to exceed 10 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.

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 over three weeks in rats, with a cumulative IV dose of 35 mg/kg. 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 DOSE AND METHOD OF ADMINISTRATION).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Alendronate did not cause gene mutations in bacteria or in mammalian cells in vitro, nor did it cause DNA damage in rat hepatocytes in vitro (alkaline elution assay). In assays of chromosomal damage, alendronate was weakly positive in an in vitro assay using Chinese hamster ovary cells at cytotoxic concentrations (greater

than or equal to 5 mm) but was negative at intravenous doses up to 25 mg/kg/day (75 mg/m^2) in an in vivo assay (chromosomal aberrations in mouse bone marrow).

Carcinogenicity

No evidence of carcinogenic effect was observed in a 105-week study in rats receiving oral doses up to 3.75 mg/kg/day and in a 92-week study in mice receiving oral doses up to 10 mg/kg/day.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Lactose monohydrate, microcrystalline cellulose, povidone, croscarmellose sodium and magnesium stearate.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Protect from moisture and light and store tablets in original blister package until use.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: Aluminium/PVC blister packs

Pack sizes: 4 tablets

Australian Register of Therapeutic Goods (ARTG)

AUST R 134702 – FONAT alendronic acid 70mg tablet blister pack

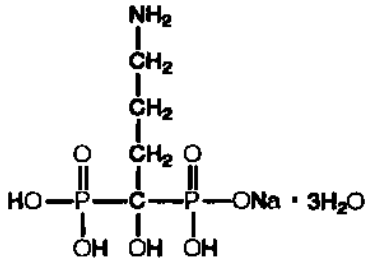
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Alendronate sodium is a white, crystalline, non-hygroscopic powder. It is soluble in water, very slightly soluble in alcohol, and practically insoluble in chloroform.

Chemical Structure



Chemical Name

(4-amino-1-hydroxybutylidene) bisphosphonic acid monosodium salt trihydrate

Molecular formula

$C_4H_{12}NNaO_7P_2 \bullet 3H_2O$

Molecular weight

325.13

CAS Number

121268-17-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

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Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

15/10/2008

10 DATE OF REVISION

09/04/2024

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial changes
3	Updated tablet description
6.5	Addition of ARTG details
8	Updated sponsor details

FONAT® is a Viatris company trade mark

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