



## New Zealand Data Sheet

### APO-ALENDRONATE

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#### Alendronate sodium 91.35mg equivalent to Alendronate 70mg Tablet

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#### Presentation

APO-ALENDRONATE 70mg tablets are white, oval (12.7mm by 7.2mm) and biconvex, identified by an engraved "APO" on one side and "ALE 70" on the other side. Each tablet typically weighs about 350mg.

#### Uses

#### Actions

Animal studies have indicated the following mode of action. At the cellular level, alendronate shows preferential localisation to sites of bone resorption specifically under osteoclasts. The osteoclasts adhere normally to the bone surface but lack the ruffled border that is indicative of active resorption. Alendronate does not interfere with osteoclast recruitment or attachment, but it does inhibit osteoclast activity. Studies in mice on the localisation of radioactive [3H] alendronate in bone showed about 10-fold higher uptake on osteoclast surfaces than on osteoblast surfaces. Bones examined 6 and 49 days after [3H] alendronate administration in rats and mice respectively showed that normal bone was formed on top of the alendronate, which was incorporated inside the matrix where it is no longer pharmacologically active. Thus, alendronate must be continuously administered to suppress osteoclasts on newly formed resorption surfaces. Histomorphometry in baboons and rats showed that alendronate treatment reduces bone turnover (i.e. number of sites at which bone is remodelled). In addition bone formation exceeds bone resorption at these remodelling sites, leading to progressive gains in bone mass.

#### Pharmacokinetics

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

#### Absorption

Relative to an intravenous (IV) 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. Oral bioavailability in men (0.6%) was similar to that in women. Bioavailability was decreased similarly (by approximately 40%) whether alendronate was administered one or one-half hour before a standardised breakfast. In osteoporosis and Paget's disease studies, alendronate was effective when administered at least 30 minutes before the first food or beverage of the day.

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

In healthy subjects, oral prednisone (20mg three times daily for 5 days) did not produce a clinically meaningful change in the oral bioavailability of alendronate (a mean increase ranging 20 to 44 %).

#### Distribution

Studies in rats show that alendronate transiently distributes to soft tissues following 1mg/kg IV administration but is then rapidly redistributed to bone or excreted in the urine. The mean steady



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state volume of distribution, exclusive of bone, is at least 28 L in humans. Concentrations of medicine in plasma following therapeutic oral doses are too low for analytical detection (less than 5ng/mL). Protein binding in human plasma is approximately 78%.

### Metabolism

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

### Elimination

Following a single IV dose of [<sup>14</sup>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 10 mg IV dose, the renal clearance of alendronate was 71 mL/min, and systemic clearance did not exceed 200 mL/min. Plasma concentrations fell by more than 95% within 6 hours following IV administration. The terminal half-life in humans is estimated to exceed 10 years, reflecting the release of alendronate from the skeleton.

### Characteristics in Patients

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

### Indications

APO-ALENDRONATE is indicated:

- In postmenopausal women for the treatment of osteoporosis to prevent fractures, including those of the hip and spine (vertebral compression fractures).
- For the treatment of osteoporosis in men to prevent fractures.

### Dosage and Administration

APO-ALENDRONATE must be taken at least one half hour 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 APO-ALENDRONATE (see Interactions).

To facilitate delivery to the stomach and thus reduce the potential for oesophageal irritation, APO-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. APO-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 Warnings and Precautions).

Patients should receive supplemental calcium and vitamin D; if dietary calcium is inadequate (see Warnings and Precautions).

No dosage adjustment is necessary for the elderly or for patients with mild-to-moderate renal insufficiency (creatinine clearance 35 to 60 mL/min). APO-ALENDRONATE is not recommended for patients with more severe renal insufficiency (creatinine clearance < 35 mL/min) due to lack of experience.



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#### Treatment of Osteoporosis in Postmenopausal Women and in Men

The recommended dosage is one 70 mg tablet once weekly

#### 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 Warnings and Precautions)

#### Warnings and Precautions

APO-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. Physicians should therefore be alert to any signs or symptoms signalling a possible oesophageal reaction and patients should be instructed to discontinue APO-ALENDRONATE and seek medical attention if they develop dysphagia, odynophagia, retrosternal pain or new or worsening heartburn.

The risk of severe oesophageal adverse experiences appears to be greater in patients who lie down after taking APO-ALENDRONATE and/or who fail to swallow it with a full glass of water, and/or who continue to take APO-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 Dosage and 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. However, a causal relationship has not been established.

Because of possible irritant effects of APO-ALENDRONATE on the upper gastrointestinal mucosa and a potential for worsening of the underlying disease, caution should be used when APO-ALENDRONATE is given to patients with active upper gastrointestinal problems, such as dysphagia, oesophageal diseases, gastritis, duodenitis, or ulcers.

To facilitate delivery to the stomach and thus reduce the potential for oesophageal irritation patients should be instructed to swallow APO-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 APO-ALENDRONATE at bedtime or before arising 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 (such as difficulty or pain upon swallowing, retrosternal pain or new or worsening heartburn) they should stop taking APO-ALENDRONATE and consult their physician.

Localised osteonecrosis of the jaw (ONJ), generally associated with tooth extraction and/or local infection with delayed healing, has been reported rarely with oral bisphosphonates (see Adverse



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Effects, Post-Marketing Experience). 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), poor oral hygiene, and co-morbid disorders (e.g., pre-existing dental disease, anaemia, coagulopathy, infection). Patients who develop ONJ should receive appropriate care by an oral surgeon.

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 Adverse Effects, *Post-Marketing Experience*). 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 drug or another bisphosphonate.

Stress fractures (also known as insufficiency fractures) of the proximal femoral shaft have been reported in patients treated long-term with alendronic acid (time to onset in the majority of cases ranged from 18 months to 10 years). The fractures occurred after minimal or no trauma and some patients experienced thigh pain, often associated with imaging features of stress fractures, weeks to months before presenting with a completed femoral fracture. Fractures were 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 was also reported. Discontinuation of bisphosphonate therapy in patients with stress fracture is advisable pending evaluation of the patient, based on an individual benefit risk assessment.

Patients should be instructed that if they miss a dose of APO-ALENDRONATE once weekly, 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.

APO-ALENDRONATE is not recommended for patients with creatinine clearance <35mL/min (see Dosage and Administration).

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

Hypocalcaemia must be corrected before initiating therapy with APO-ALENDRONATE (see Contraindications). Other disorders affecting mineral metabolism (such as 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 APO-ALENDRONATE.

Due to the positive effects of APO-ALENDRONATE in increasing bone mineral, 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.

### **Pregnancy**

Category B3



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APO-ALENDRONATE has not been studied in pregnant women and should not be given to them.

### **Nursing Mothers**

APO-ALENDRONATE has not been studied in breast-feeding women and should not be given to them.

### **Paediatric Use**

APO-ALENDRONATE has not been studied in children and should not be given to them.

### **Use in the Elderly**

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

### **Effects on the Ability to Drive and Use Machines**

There are no data to suggest that APO-ALENDRONATE affects the ability to drive or use machines.

### **Animal Toxicology**

#### **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.

#### **Mutagenesis**

Alendronate was not genotoxic in the *in vitro* microbial mutagenesis assay with and without metabolic activation. Similarly, no evidence of mutagenicity was observed in an *in vitro* mammalian cell mutagenesis assay, an *in vitro* alkaline elution assay in rat hepatocytes, and an *in vivo* chromosomal aberration assay in mice at IV doses up to 25 mg/kg/day (75 mg/m<sup>2</sup>). In an *in vitro* chromosomal aberration assay in Chinese hamster ovary cells, however, alendronate was weakly positive at concentrations >5 mM in the presence of cytotoxicity. This is of no relevance to safety in humans since similar concentrations are not achievable *in vivo* at therapeutic doses. Furthermore, clear negative results in four of five genotoxicity studies, including the most relevant studies for human carcinogenic potential (the *in vivo* chromosomal aberration assay and the microbial mutagenesis assay), and negative carcinogenicity studies in rats and mice lead to the conclusion that there is no evidence of genotoxic or carcinogenic risks from alendronate in humans.

#### **Reproduction**

Alendronate had no effect on fertility or reproductive performance (male or female) in rats at oral doses up to 5 mg/kg/day. The only medicine-related effect seen in these studies was difficulty in parturition in rats, which is directly related to pharmacologically mediated hypocalcaemia. This effect can be prevented in rats by calcium supplementation. Furthermore, a clear no-effect level of 1.25 mg/kg/day was established.

#### **Development**

In developmental toxicity studies, there were no adverse effects at doses up to 25 mg/kg/day in rats and 35 mg/kg/day in rabbits.



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### Adverse Effects

#### Clinical Studies

In clinical studies alendronate was generally well tolerated. In studies of up to 5 years duration adverse effects which usually were mild generally did not require discontinuation of therapy.

#### Treatment of Osteoporosis

##### Postmenopausal Women

In two, three-year, placebo-controlled, double-blind, multicentre studies (United States and Multinational) of virtually identical design, the overall safety profiles of alendronate 10 mg/day and placebo were similar. The following upper gastrointestinal adverse experiences were reported by the investigators as possibly, probably, or definitely medicine related in > 1% of patients treated with alendronate 10 mg/day and at a greater incidence than in patients treated with placebo: abdominal pain (alendronate, 6.6% vs placebo, 4.8%), dyspepsia (3.6%, 3.5%), oesophageal ulcer (1.5%, 0.0%), dysphagia (1.0%, 0.0%), and abdominal distention (1.0%, 0.8%).

Rarely, rash and erythema have occurred.

Additionally, the following adverse experiences were reported by the investigators as possibly, probably or definitely medicine related in  $\geq$  1% of patients treated with alendronate 10 mg/day and at a greater incidence than in patients treated with placebo: musculoskeletal (bone, muscle or joint) pain (alendronate, 4.1% vs placebo 2.5%), constipation (3.1%, 1.8%), diarrhoea (3.1%, 1.8%), flatulence (2.6%, 0.5%), and headache (2.6%, 1.5%).

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 a one year, double-blind, multicenter study, the overall safety and tolerability profiles of alendronate once weekly 70 mg (n=519) and alendronate 10 mg daily (n=370) were similar. The following adverse experiences were reported by the investigators as possibly, probably, or definitely medicine related in  $\geq$  1% of patients in either treatment group: abdominal pain (alendronate once weekly 70 mg, 3.7%; alendronate 10 mg daily, 3.0%), musculoskeletal (bone, muscle or joint) pain (2.9%, 3.2%), dyspepsia (2.7%, 2.2%), acid regurgitation (1.9%, 2.4%), nausea (1.9%, 2.4%), abdominal distention (1.0%, 1.4%), constipation (0.8%, 1.6%), flatulence (0.4%, 1.6%), muscle cramp (0.2%, 1.1%), gastritis (0.2%, 1.1%), and gastric ulcer (0.0%, 1.1%).

##### Men

In two, placebo-controlled, double blind, multicenter studies in men (a two year study of alendronate 10 mg/day (n = 146) and a one year study of alendronate once weekly 70 mg (n = 109), the safety profile of alendroante was generally similar to that seen in post menopausal women. The rates of discontinuation of therapy due to any clinical adverse experience were 2.7% for alendronate 10 mg/day vs. 10.5% for placebo, and 6.4% for alendroante once weekly 70 mg vs. 8.6% for placebo.

##### Other Studies in Men and Women

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



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

#### Post-Marketing Experience

The following adverse reactions have been reported in post-marketing use:

*Body as a Whole:* hypersensitivity reactions including urticaria and rarely, angioedema. As with other bisphosphonates, transient symptoms as in an acute-phase response (myalgia, malaise 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.

*Gastrointestinal:* nausea, vomiting, oesophagitis, oesophageal erosions, oesophageal ulcers, rarely oesophageal stricture or perforation, and oropharyngeal ulceration; rarely gastric or duodenal ulcers, some severe and with complications, although a causal relationship has not been established (see Warnings and Precautions, and Dosage and Administration). Localised osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection, with delayed healing, has been reported rarely (see Warnings and Precautions).

*Musculoskeletal:* bone, joint, and/or muscle pain, rarely severe and/or incapacitating. Stress fractures (insufficiency fractures) of the proximal femoral shaft have been reported in patients treated long-term with alendronic acid (see Warnings and Precautions).

*Skin:* rash (occasionally with photosensitivity), pruritus, rarely severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis.

*Special Senses:* rarely uveitis, scleritis or episcleritis.

#### Laboratory Test Findings

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 mgP/dL (0.65 mM) were similar in both treatment groups.

#### Interactions

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

No other medicine interactions of clinical significance are anticipated.

Concomitant use of HRT (oestrogen ± 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



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and tolerability profile of the combination was consistent with those of the individual treatments (see Adverse Effects, Clinical Studies, Concomitant use with oestrogen/hormone replacement therapy).

Specific interaction studies were not performed. Alendronate was used in osteoporosis studies in men, postmenopausal women and glucocorticoid users, with a wide range of commonly prescribed medicines (including NSAIDs) without evidence of clinical adverse interactions.

In a three year controlled clinical study (n=2027) during which a majority of patients received concomitant NSAIDs, the incidence of ulcer-related adverse events was similar in patients taking alendronate 5 or 10 mg compared to those taking placebo.

However, the incidence of upper gastrointestinal adverse events was increased in the patients receiving daily therapy with dosages of alendronate greater than 10 mg and aspirin-containing products in other clinical studies. However this was not observed in studies with alendronate once weekly 70 mg.

### Overdosage

No specific information is available on the treatment of overdosage with APO-ALENDRONATE. Hypocalcaemia, hypophosphataemia and upper gastrointestinal adverse events, such as upset stomach, heartburn, oesophagitis, gastritis, or ulcer, may result from oral overdosage. Milk or antacids should be given to bind alendronate. Due to the risk of oesophageal irritation, vomiting should not be induced and the patient should remain fully upright.

### Pharmaceutical Precautions

Store at or below 25°C.  
Protect from heat, light and moisture.  
Shelf life of 3 years from the date of manufacture.

### Medicine Classification

Prescription Medicine

### Package Quantities

Blister packs of 100 tablets  
Bottle packs of 100 tablets

### Further Information

APO-ALENDRONATE tablets are Lactose and Gluten free.

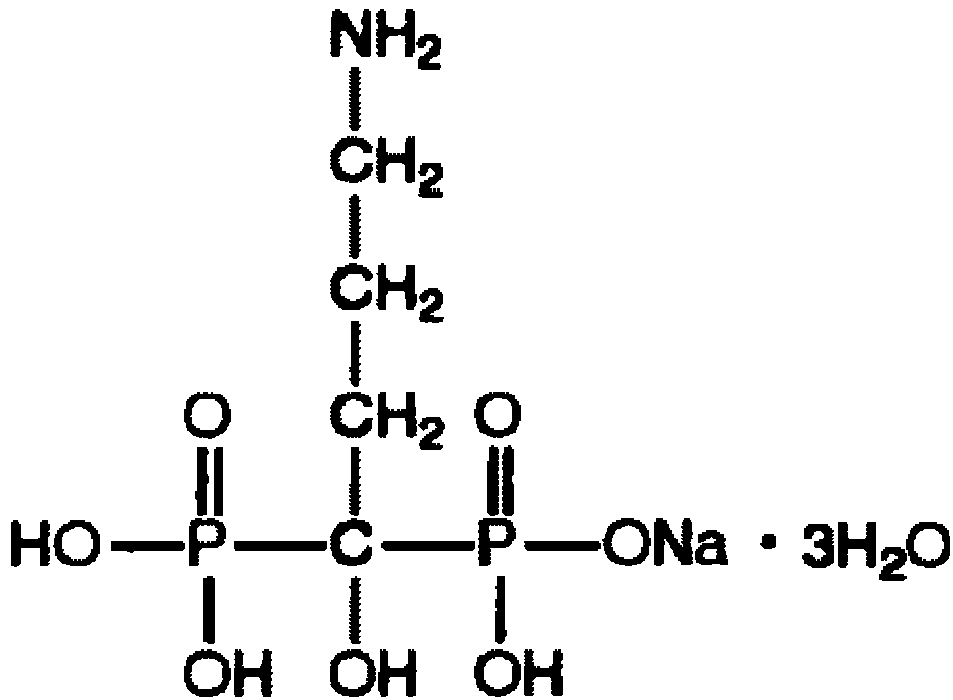
### Chemistry

APO-ALENDRONATE tablets contain alendronate sodium, which is described chemically as: (4-amino-1-hydroxybutylidene) bisphosphonic acid monosodium salt trihydrate. The empirical formula is  $C_4H_{12}NNaO_7P_2 \cdot 3H_2O$ . The formula weight is 325.12. The structural formula is:



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Alendronate is a white, crystalline, nonhygroscopic powder. It is soluble in water, very slightly soluble in alcohol and practically insoluble in chloroform.

### Name and Address

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### Date of Preparation

26 August 2010