NEW ZEALAND DATA SHEET

1 PRODUCT NAME

FOSAMAX® 70 mg once weekly tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Alendronate sodium 70 mg tablets.

List of excipients with known effect:

- lactose

For the full list of excipients, see **Section 6.1 List of excipients.**

3 PHARMACEUTICAL FORM

A white oval tablet with the outline of a bone image on one side and 31 on the other. Dimensions are 12.7 mm x 5.542 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

FOSAMAX 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.

4.2 Dose and method of administration

Dose

Treatment of Osteoporosis in Postmenopausal Women and in Men
The recommended dosage is one 70 mg tablet once weekly.

Special populations

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

Paediatric population

See **Section 4.4 Special warnings and precautions for use, Paediatric population.**

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

Method of administration

FOSAMAX 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 FOSAMAX (see **Section 4.5 Interactions with other medicines and other forms of interactions**).

To facilitate delivery to the stomach and thus reduce the potential for oesophageal irritation,

FOSAMAX 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. FOSAMAX 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**).

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 the active substance or to any of the excipients listed in **Section 6.1 List of excipients**.
- Hypocalcaemia (see **Section 4.4 Special warnings and precautions for use**).

4.4 Special warnings and precautions for use

FOSAMAX, 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 FOSAMAX. 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 FOSAMAX 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 FOSAMAX and/or who fail to swallow it with a full glass of water, and/or who continue to take FOSAMAX 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 FOSAMAX on the upper gastrointestinal mucosa and a potential for worsening of the underlying disease, caution should be used when FOSAMAX is given to patients with active upper gastrointestinal problems, such as dysphagia, oesophageal diseases (including known Barrett's oesophagus), gastritis, duodenitis, or ulcers.

To facilitate delivery to the stomach and thus reduce the potential for oesophageal irritation patients should be instructed to swallow FOSAMAX 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 FOSAMAX 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 FOSAMAX and consult their physician.

Localised osteonecrosis of the jaw (ONJ), generally associated with tooth extraction and/or local infection (including osteomyelitis) with delayed healing, has been reported rarely with oral bisphosphonates (see **Section 4.8 Undesirable 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, angiogenesis inhibitors), poor oral hygiene, co-morbid disorders (e.g. periodontal and/or other pre-existing

dental disease, anaemia, coagulopathy, infection) and smoking. Patients who develop ONJ should receive appropriate care by an oral surgeon and discontinuation of bisphosphonate therapy should be considered based on individual benefit/risk assessment. Dental surgery may exacerbate the condition.

For patients requiring invasive dental surgery (e.g. tooth extraction, dental implants), clinical judgment of the treating physician and/or oral surgeon should guide the management plan, including bisphosphonate treatment, of each patient based on individual benefit/risk assessment.

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 Undesirable 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 medicine or another bisphosphonate.

Low-energy fractures of the subtrochanteric and proximal femoral shaft and other bones have been reported in a small number of long-term (usually longer than three years) bisphosphonate-treated patients. Some were stress fractures (some of which were reported as insufficiency fractures) occurring in the absence of apparent trauma or induced by mild external force. 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 the reported femur fractures were bilateral; therefore the contralateral femur should be examined in patients who have sustained a femoral shaft stress fracture. Stress fractures with similar clinical features also have occurred in patients not treated with bisphosphonates. 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. Interruption of bisphosphonate therapy in patients with stress fractures should be considered, pending evaluation of the patient, based on individual benefit/risk assessment.

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

Hypocalcaemia must be corrected before initiating therapy with FOSAMAX (see **Section 4.3 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 FOSAMAX.

Due to the positive effects of FOSAMAX in increasing bone mineral, small, asymptomatic decreases in serum calcium and phosphate may occur, especially in patients with Paget's disease, in whom the pre-treatment 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.

Renal impairment

FOSAMAX is not recommended for patients with creatinine clearance < 35 mL/min (see **Section 4.2 Dose and method of administration**).

Paediatric population

FOSAMAX is not indicated for use in children.

Use in the elderly

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

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 absorption of FOSAMAX. Therefore, patients must wait at least one half hour after taking FOSAMAX before taking any other oral medication.

No other medicine interactions of clinical significance are anticipated.

Concomitant use of HRT (oestrogen ± progestin) and FOSAMAX was assessed in two clinical studies of one or two years' duration in postmenopausal osteoporotic women. Combined use of FOSAMAX 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 Undesirable effects, Clinical Studies, Concomitant use with oestrogen/hormone replacement therapy**).

Specific interaction studies were not performed. FOSAMAX was used in osteoporosis studies in men, postmenopausal women and glucocorticoid users, with a wide range of commonly prescribed medicines 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 FOSAMAX 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 FOSAMAX greater than 10 mg and aspirin- containing products in other clinical studies. However this was not observed in studies with FOSAMAX once weekly 70 mg.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

FOSAMAX has not been studied in pregnant women and should not be given to them.

Breast-feeding

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

Fertility

See **Section 5.3 Preclinical safety data, Animal Toxicology, Reproduction.**

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, certain adverse reactions that have been reported with FOSAMAX may affect some patients' ability to drive or operate machinery. Individual responses to FOSAMAX may vary (see **Section 4.8 Undesirable effects**).

4.8 Undesirable effects

Clinical Studies

In clinical studies FOSAMAX 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 FOSAMAX 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 FOSAMAX 10 mg/day and at a greater incidence than in patients treated with placebo: abdominal pain (FOSAMAX, 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 ≥ 1% of patients treated with FOSAMAX 10 mg/day and at a greater incidence than in patients treated with placebo: musculoskeletal (bone, muscle or joint) pain (FOSAMAX, 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 FOSAMAX 10 mg/day was similar to that observed during the three-year placebo-controlled period. Additionally, the proportion of patients who discontinued FOSAMAX 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, multicentre study, the overall safety and tolerability profiles of FOSAMAX once weekly 70 mg (n=519) and FOSAMAX 10 mg daily (n=370) were similar. The following adverse experiences were reported by the investigators as possibly, probably, or definitely medicine related in ≥ 1% of patients in either treatment group: abdominal pain (FOSAMAX once weekly 70 mg, 3.7%; FOSAMAX 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 distension (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, multicentre studies in men (a two year study of FOSAMAX 10 mg/day (n = 146) and a one year study of FOSAMAX once weekly 70 mg (n = 109), the safety profile of FOSAMAX 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 FOSAMAX 10 mg/day vs. 10.5% for placebo, and 6.4% for FOSAMAX 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 FOSAMAX once weekly 70 mg and placebo.

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

Prevention of Osteoporosis in Postmenopausal Women

The safety of FOSAMAX in postmenopausal women 40-60 years of age has been evaluated in three double- blind, placebo-controlled studies involving over 1,400 patients randomised to receive FOSAMAX for either two or three years. In these studies, the safety and tolerability profile of FOSAMAX 5 mg/day (n = 642) was similar to that of placebo (n = 648). The only adverse experience reported by the investigators as possibly, probably or definitely medicine

related in ≥ 1% of patients treated with FOSAMAX 5 mg/day and at a greater incidence than placebo was dyspepsia (FOSAMAX, 1.9% vs. placebo, 1.7%).

Concomitant use with oestrogen/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 FOSAMAX 10 mg once daily and oestrogen ± progestin (n = 354) was consistent with those of the individual treatments.

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 FOSAMAX 5 and 10 mg/day were generally similar to that of placebo. The following gastrointestinal adverse experiences were reported by the investigators as possibly, probably, or definitely medicine related in ≥ 1% of patients treated with either FOSAMAX 5 or 10 mg/day and at a greater incidence than placebo: abdominal pain (FOSAMAX 10 mg, 3.2%; FOSAMAX 5 mg, 1.9%; placebo, 0.0%), acid regurgitation (2.5%, 1.9%, 1.3%), constipation (1.3%, 0.6%, 0.0%), melena (1.3%, 0.0%, 0.0%) and nausea (0.6%, 1.2%, 0.6%).

The overall safety and tolerability profile in the glucocorticoid-induced osteoporosis population that continued therapy for the second year of the studies was consistent with that observed in the first year.

Paget's Disease of Bone
In clinical studies (Paget's disease and osteoporosis), adverse experiences reported in patients taking FOSAMAX 40 mg/day for 3-12 months were similar to those in postmenopausal women treated with FOSAMAX 10 mg/day. However, there was an apparent increased incidence of upper gastrointestinal adverse experiences in patients taking FOSAMAX 40 mg/day. Isolated cases of oesophagitis and gastritis resulted in discontinuation of treatment.

Additionally, musculoskeletal (bone, muscle or joint) pain, which has been described in patients with Paget's disease treated with other bisphosphonates, was reported by the investigators as possibly, probably, or definitely medicine related in approximately 6% of patients treated with FOSAMAX 40 mg/day versus approximately 1% of patients treated with placebo, but rarely resulted in discontinuation of therapy.

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, asthenia and rarely, fever) have been reported with FOSAMAX, 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; 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), with delayed healing has been reported rarely (see **Section 4.4 Special warnings and precautions for use**).

Musculoskeletal: bone, joint, and/or muscle pain, rarely severe and/or incapacitating (see **Section 4.4 Special warnings and precautions for use**); joint swelling; low-energy fractures of the femoral shaft and other bones (see **Section 4.4 Special warnings and precautions for use**).

Nervous System: dizziness, vertigo, dysgeusia.

Skin: rash (occasionally with photosensitivity), pruritus, alopecia, 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.

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 FOSAMAX 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.

Reporting of suspected adverse reactions

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 https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

No specific information is available on the treatment of overdosage with FOSAMAX. 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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Bisphosphonates, ATC code: M05BA04

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

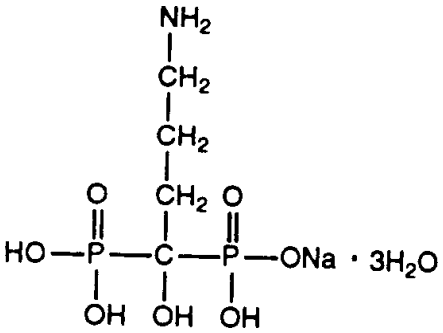
Mechanism of action

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 [^{3}H] alendronate in bone showed about 10-fold higher uptake on osteoclast surfaces than on osteoblast surfaces. Bones examined 6 and 49 days after [^{3}H] 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.

Chemistry

FOSAMAX 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:



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

5.2 Pharmacokinetic properties

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, FOSAMAX was effective when administered at least 30 minutes before the first food or beverage of the day.

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

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

The oral bioavailability in children (4 to 16 years of age) with osteogenesis imperfecta (OI) was similar to that observed in adults (see **Section 4.4 Special warnings and precautions for use, Paediatric population**).

Distribution

Studies in rats show that alendronate transiently distributes to soft tissues following 1 mg/kg IV 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 medicine in plasma following therapeutic oral doses are too low for analytical detection (less than 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 IV 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 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 **Section 4.2 Dose and method of administration**).

5.3 Preclinical safety data

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^2). 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each FOSAMAX tablet contains the following inactive ingredients: cellulose-microcrystalline, lactose, croscarmellose sodium and magnesium stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

FOSAMAX 70 mg tablets are available in packs of 4 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Medicine

8 SPONSOR

Organon (New Zealand) Limited

Level 7, 36 Brandon Street

Wellington 6100
Tel: 0800 111 700

9 DATE OF FIRST APPROVAL

5 December 1996

10 DATE OF REVISION

17 April 2023

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4, 4.8	Added “low energy fractures of other bones” as a Precaution and Post Marketing Adverse Event.

S-WPC-OG0217-MF-012023