Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Fosamax 10mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of 'Fosamax' 10mg contains 13.05mg of alendronate sodium, which is the molar equivalent to 10mg of alendronic acid.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Tablet.
'Fosamax' 10mg is supplied as oval white tablets, marked '936' on one side and plain on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

In post-menopausal women with osteoporosis, 'Fosamax' is indicated for the treatment of osteoporosis to prevent fractures, including those of the hip and spine (vertebral compression fractures).

'Fosamax' is indicated for the treatment of osteoporosis in men to prevent fractures.

'Fosamax' is indicated for the treatment and prevention of glucocorticoid-induced osteoporosis in men and women.

In post-menopausal women who are at risk of developing osteoporosis 'Fosamax' is indicated for the prevention of osteoporosis to reduce the risk of future fracture.

4.2 Posology and method of administration

- Treatment of osteoporosis in post-menopausal women*:* The recommended dosage is 10 mg once a day.

- Treatment of osteoporosis in men*:* The recommended dosage is 10 mg once a day.

- Treatment and prevention of glucocorticoid-induced osteoporosis*:* For post-menopausal women not receiving hormone replacement therapy (HRT) with an oestrogen, the recommended dosage is 10 mg once a day.

For other patients (i.e. men, pre-menopausal women and post-menopausal women receiving HRT with an oestrogen), the recommended dosage is 5 mg once a day.

- Prevention of osteoporosis in post-menopausal women: The recommended dosage is 5 mg once a day.

- To permit adequate absorption of 'Fosamax'*:* 'Fosamax' 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 'Fosamax' *(see 4.5 'Interaction with other medicaments and other forms of interaction').*

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

- ‘Fosamax’ should only be swallowed upon rising for the day with a full glass of water (not less than 200 ml or 7fl.oz.).
- Patients should only swallow 'Fosamax' whole. Patients should not crush or chew the tablet or allow the tablet to dissolve in their mouths because of a potential for oropharyngeal ulceration.
- Patients should not lie down for at least 30 minutes after taking ‘Fosamax’.
- Patients should not lie down until after their first food of the day, which should be at least 30 minutes after taking the tablet.
- ‘Fosamax’ should not be taken at bedtime or before rising for the day.

All patients with osteoporosis should receive supplemental calcium and vitamin D if dietary intake is inadequate *(see 4.4 ‘Special warnings and precaution for use’).*

- Use in the elderly: In clinical studies, there was no age-related difference in the efficacy or safety profiles of ‘Fosamax’. Therefore, no dosage adjustment is necessary for the elderly.

- Use in renal impairment*:* No dosage adjustment is necessary for patients with mild-to-moderate renal insufficiency (creatinine clearance 35-60 ml/min). ‘Fosamax’ is not recommended for patients with more severe renal insufficiency (creatinine clearance <35 ml/min).

- Use in children (under 18 years): Aldronate has been studied in a small number of patients with osteogenesis imperfecta under 18 years of age. Results are insufficient to support its use in children.

- Use in hepatic impairment: No dosage adjustment is necessary *(see 5.2 ‘Pharmacokinetic properties’, biotransformation).*

Clinical experience with ‘Fosamax’ is available for a period of five years: extension studies are ongoing. The effects of longer-term therapy are unknown.

4.3 Contraindications

- Abnormalities of the oesophagus and other factors which delay oesophageal emptying, such as stricture or achalasia.
- Inability to stand or sit upright for at least 30 minutes.
- Hypersensitivity to any component of this product.
- Hypocalcaemia *(see 4.4 ‘Special warnings and precautions for use’)*

4.4 Special warnings and precautions for use

This product contains a novel drug substance. Any side-effects or adverse drug reactions associated with its use should be reported.

‘Fosamax’ can cause local irritation of the upper gastro-intestinal mucosa. Because there is a potential for worsening of the underlying disease, caution should be used when ‘Fosamax’ is given to patients with active upper gastro-intestinal problems, such as dysphagia, oesophageal disease, gastritis, duodenitis, or ulcers or with a recent history (within the previous year) of major gastro-intestinal disease such as peptic ulcer, or active gastro-intestinal bleeding, or surgery of the upper gastro-intestinal tract other than pyloroplasty *(see 4.3 Contraindications’).* In patients with known Barrett's oesophagus, prescribers should consider the benefits and potential risks of alendronate on an individual patient basis.

Oesophageal reactions (sometimes severe and requiring hospitalisation), such as oesophagitis, oesophageal ulcers and oesophageal erosions, rarely followed by oesophageal stricture or perforation, have been reported in patients receiving ‘Fosamax’. 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 symptoms of oesophageal irritation such as dysphagia, pain on swallowing, retrosternal pain, or new or worsening heartburn.

The risk of severe oesophageal adverse experience appears to be greater in patients who fail to take 'Fosamax' properly and/or who continue to take 'Fosamax' after developing symptoms suggestive of oesophageal irritation. It is very important that the full dosing instructions are provided to, and understood by the patient, *(see 4.2 'Posology and method of administration').* Patients should be informed that failure to follow these instructions may increase their risk of oesophageal problems.

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

Osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection (including osteomyelitis) has been reported in patients with cancer receiving treatment regimes including primarily intravenously administration bisphosphonates. Many of these patients were also receiving chemotherapy and corticosteroids. Osteonecrosis of the jaw has also been reported in patients with osteoporosis receiving oral bisphosphonates.

A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, chemotherapy, radiotherapy, corticosteroids, poor oral hygiene, periodontal disease).

While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop osteonecrosis of the jaw while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of the jaw.

Clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

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 4.8 undersirable effects)*. The time to onset of symptoms varied from one day to several months after starting treatment. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when rechallanged with the same drug or another bisphosphonate.

'Fosamax' is not recommended for patients with severe renal insufficiency *(see 4.2 Posology and method of administration').*

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

Hypocalcaemia must be corrected before initiating therapy with 'Fosamax' *(see 4.3 'Contraindications').* Other disorders affecting mineral metabolism (such as vitamin D deficiency and hypoparathyroidism) should also be effectively treated. In patients with these conditions, serum calcium and symptoms of 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 receiving glucocorticoids, in whom calcium absorption may be decreased. These are usually small and asymptomatic. However, there have been rare reports of symptomatic hypocalcemia, which have occasionally been severe and often occurred in patients with predisposing conditions (e.g. hypoparathyroidism, vitamin D deficiency and calcium malabsorption). Ensuring adequate calcium and vitamin D intake is therefore particularly important in patients receiving glucocorticoids.

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

4.5 Interaction with other medicinal products and other forms of interaction

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 30 minutes after taking 'Fosamax' before taking any

other oral medication.

No other drug interactions of clinical significance are anticipated.

No other interactions with medicinal products of clinical significance are anticipated. A number of patients in the clinical trials received ostrogen (intravaginal, transdermal, or oral) while taking alendronate. No adverse experiences attributable to their concomitant use were identified.

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

Although specific interaction studies were not performed, in clinical studies alendronate was used concomitantly with a wide range of commonly prescribed medicinal products without evidence of clinical adverse interactions.

4.6 Fertility, pregnancy and lactation

Use during pregnancy
'Fosamax' should not be used during pregnancy. There are no adequate data from the use of alendronate in pregnant women. Animal studies do not indicate direct harmful effects with respect to pregnancy, embryonic/fetal development, or postnatal development. Alendronate given during pregnancy in rats caused dystocia related to hypocalcemia (see 5.3 'Preclinical safety data')

Use during lactation
It is not known whether 'Fosamax' is excreted into human breast milk. Fosomax should not be used by breast-feeding women.

4.7 Effects on ability to drive and use machines

No studies 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 4.8 Undesirable effects).

4.8 Undesirable effects

'Fosamax' has been studied in nine major clinical studies (n=5,886). In the longest running trials in post-menopausal women up to five years experience has been collected. Two years safety data are available in both men with osteoporosis and men and women on glucocorticoids.

The following adverse experiences have also been reported during clinical studies and/or post-marketing use:

[Common (≥1/100, <1/10), Uncommon (≥1/1000, <1/100), Rare (≥10,000, <1/1000), Very rare (<1/10,000 including isolated cases)]

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

Metabolism and nutrition disorders:
Rare: symptomatic hypocalcaemia, often in association with predisposing conditions. (see section 4.4)

Nervous system disorders:
Common: headache

Eye disorders:
Rare: uveitis, scleritis, episcleritis

Gastrointestinal disorders:
Common: abdominal pain, dyspepsia, constipation, diarrhoea, flatulence, oesophageal, ulcer*, dysphagia*, abdominal distension, acid regurgitation

Uncommon: nausea, vomiting, gastritis, oesophagitis*, oesophageal erosions*, melena

Rare: oesophageal stricture*, oropharyngeal ulceration*, upper gastrointestinal PUBs (perforation, ulcers, bleeding) (see section 4.4)
*see sections 4.2 and 4.4

Skin and subcutaneous tissue disorders:
Uncommon: rash, pruritus, erythema

Rare: rash with photosensitivity

Very rare and isolated cases: isolated cases of severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis

Musculoskeletal, connective tissue and bone disorders:
Common: musculoskeletal (bone, muscle or joint) pain

Rare: Osteonecrosis of the jaw has been reported in patients treated by bisphosphonates. The majority of the reports refer to cancer patients, but such cases have also been reported in patients treated for osteoporosis. Osteonecrosis of the jaw is generally associated with tooth extraction and / or local infection (including osteomyelitis). Diagnosis of cancer, chemotherapy, radiotherapy, corticosteroids, poor oral hygiene are also deemed as risk factors; severe musculoskeletal (bone, muscle or joint) pain (see 4.4 ‘Special warnings and precautions for use’).

General disorders and administrative site conditions:
Rare: transient symptoms as in an acute-phase response (myalgia, malaise and rarely, fever), typically in association with initiation of treatment.

During post-marketing experience the following reactions have been reported (frequency unknown):

Nervous system disorders: dizziness, dysgeusia

Ear and labyrinth disorders: vertigo

Skin and subcutaneous tissue disorders: alopecia

Musculoskeletal, connective tissue and bone disorders: joint swelling

General disorders and administrative site conditions: asthenia, peripheral oedema

Laboratory test findings
In clinical studies, asymptomatic, mild and transient decreases in serum calcium and phosphate were observed in approximately 18% and 10%, respectively, of patients taking ‘Fosamax’ versus approximately 12% and 3% of those taking placebo. However, the incidences of decreases in serum calcium to <2.0mmol/l and serum phosphate to ≤0.65 mmol/l were similar in both treatment groups.

4.9 Overdose

Significant lethality after single oral doses was seen in female rats and mice at 552 mg/kg (3,256 mg/m^2) and 966 mg/kg (2,898 mg/m^2) (2,760 and 4,830* times include the recommended dose for the treatment of osteoporosis in post-menopausal women), respectively. In males, these values were slightly higher, 626 and 1,280 mg/kg, respectively. There was no lethality in dogs at oral doses up to 200 mg/kg (4,000 mg/m^2) (1,000 times* the recommended dose for

the treatment of osteoporosis in post-menopausal women).

No specific information is available on the treatment of overdosage with 'Fosamax'. Hypocalcaemia, hypophosphataemia and upper gastro-intestinal 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. Owing to the risk of oesophageal irritation, vomiting should not be induced and the patient should remain fully upright.

***Based on a patient weight of 50 kg**

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

'Fosamax' is a bisphosphonate that inhibits osteoclastic bone resorption with no direct effect on bone formation. The bone formed during treatment with 'Fosamax' is of normal quality.

Treatment of post-menopausal osteoporosis*:*

The effects of 'Fosamax' on bone mass and fracture incidence in post-menopausal women were examined in two initial efficacy studies of identical design (n=994) as well as in the Fracture Intervention Trial (FIT: n=6,459).

In the initial efficacy studies, the mean bone mineral density (BMD) increases with 'Fosamax' 10 mg/day relative to placebo at three years were 8.8%, 5.9% and 7.8% at the spine, femoral neck and trochanter, respectively. Total body BMD also increased significantly. There was a 48% reduction in the proportion of patients treated with 'Fosamax' experiencing one or more vertebral fractures relative to those treated with placebo. In the two-year extension of these studies BMD at the spine and trochanter continued to increase and BMD at the femoral neck and total body were maintained.

FIT consisted of two placebo-controlled studies: a three-year study of 2,027 patients who had at least one baseline vertebral (compression) fracture and a four-year study of 4,432 patients with low bone mass but without a baseline vertebral fracture, 37% of whom had osteoporosis as defined by a baseline femoral neck BMD at least 2.5 standard deviations below the mean for young, adult women. In all FIT patients with osteoporosis from both studies, 'Fosamax' reduced the incidence of: ≥1 vertebral fracture by 48%, multiple vertebral fractures by 87%, ≥1 painful vertebral fracture by 45%, any painful fracture by 31% and hip fracture by 54%.

Overall these results demonstrate the consistent effect of 'Fosamax' to reduce the incidence of fractures, including those of the spine and hip, which are the sites of osteoporotic fracture associated with the greatest morbidity.

Prevention of post-menopausal osteoporosis:

The effects of 'Fosamax' to prevent bone loss were examined in two studies of post-menopausal women aged ≤60 years. In the larger study of 1,609 women (≥6 months post-menopausal) those receiving 'Fosamax' 5 mg daily for two years had BMD increases of 3.5%, 1.3%, 3.0% and 0.7% at the spine, femoral neck, trochanter and total body, respectively. In the smaller study (n=447), similar results were observed in women (6 to 36 months post-menopausal) treated with 'Fosamax' 5 mg daily for three years. In contrast, in both studies, women receiving placebo lost bone mass at a rate of approximately 1% per year. The longer term effects of 'Fosamax' in an osteoporosis prevention population are not known but clinical trial extensions of up to 10 years of continuous treatment are currently in progress.

Concomitant use with oestrogen/hormone replacement therapy (HRT):

The effects on BMD of treatment with 'Fosamax' 10 mg once-daily and conjugated oestrogen (0.625 mg/day) either alone or in combination were assessed in a two-year study of hysterectomised, post-menopausal, osteoporotic women. At two years, the increases in lumbar spine BMD from baseline were significantly greater with the combination (8.3%) than with either oestrogen or 'Fosamax' alone (both 6.0%).

The effects of BMD when ‘Fosamax’ was added to stable doses (for at least one year) of HRT (oestrogen ± progestin) were assessed in a one-year study in post-menopausal, osteoporotic women. The addition of ‘Fosamax’ 10 mg once-daily to HRT produced, at one year, significantly greater increases in lumbar spine BMD (3.7%) vs. 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.

Treatment of osteoporosis in men

The efficacy of ‘Fosamax’ 10 mg once daily in men (ages 31 to 87; mean, 63) with osteoporosis was demonstrated in a two-year study. At two years, the mean increases relative to placebo in BMD in men receiving ‘Fosamax’ 10 mg/day were: lumbar spine, 5.3%; femoral neck, 2.6%; trochanter, 3.1%; and total body, 1.6%. ‘Fosamax’ was effective regardless of age, race, gonadal function, baseline rate of bone turnover, or baseline BMD. Consistent with much larger studies in post-menopausal women, in these men, ‘Fosamax’ 10 mg/day reduced the incidence of new vertebral fracture (assessed by quantitative radiography) relative to placebo (0.8% vs. 7.1%) and, correspondingly, also reduced height loss (-0.6 vs. 2.4mm).

Glucocorticoid-induced osteoporosis:

The efficacy of ‘Fosamax’ 5 and 10 mg once-daily in men and women receiving at least 7.5 mg/day of prednisone (or equivalent) was demonstrated in two, one-year studies. At one year, the mean increases relative to placebo in BMD in patients receiving ‘Fosamax’ 5 mg/day from the combined studies were: lumbar spine, 2.4%; femoral neck, 2.2%; and trochanter, 1.6%. Total body BMD was maintained with this dose of ‘Fosamax’. The increases in BMD with ‘Fosamax’ 10 mg/day were similar to those with ‘Fosamax’ 5 mg/day in all patients except for those post-menopausal women not receiving oestrogen therapy. In these women, the increases (relative to placebo) with ‘Fosamax’ 10 mg/day were greater than those with ‘Fosamax’ 5 mg/day at the lumbar spine (4.1% vs. 1.6%) and trochanter (2.8% vs. 1.7%), but not at other sites. ‘Fosamax’ was effective regardless of dose or duration of glucocorticoid use.

The majority of patients from these studies who remained on at least 7.5 mg/day of prednisone or equivalent continued into a one-year extension. After two years of treatment, spine BMD increased by 3.7% and 5.0% relative to placebo with ‘Fosamax’ 5 and 10 mg/day respectively. Significant increases in BMD (relative to placebo) were also observed at the femoral neck, trochanter, and total body.

When the data from the three dosage groups (5 or 10 mg for two years or 2.5 mg for one year followed by 10 mg for one year) was pooled, there was a significant reduction in the incidence of patients with a new vertebral fracture at two years (‘Fosamax’, 0.7% vs placebo, 6.8%).

5.2 Pharmacokinetic properties

Absorption

Relative to an intravenous (IV) reference dose, the oral bioavailability of alendronate in women was 0.7% for doses ranging from 5 to 40 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 hour or half an hour before a standardised breakfast. In osteoporosis 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 five days) did not produce a clinically meaningful change in the oral bioavailability of alendronate (a mean increase ranging from 20 to 44%).

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 litres in humans. Concentrations of drug in plasma following therapeutic oral doses are too low for analytical detection (< 5 ng/ml). Protein binding in human plasma is approximately 78%.

Biotransformation

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

Elimination

Following a single 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. 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 ten years, reflecting release of alendronate from the skeleton. Alendronate is not excreted through the acidic or basic transport systems of the kidney in rats, and thus it is not anticipated to interfere with the excretion of other drugs by those systems in humans.

Characteristics in patients

Preclinical studies show that the drug 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 4.2 'Posology and method of administration').*

5.3 Preclinical safety data

No additional relevant information.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Anhydrous lactose
Croscarmellose sodium
Magnesium stearate
Carnauba wax

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Blister packs of opaque PVC lidded with an aluminium foil.
Pack size: 28 tablets.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA 35/83/1

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