Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Fostepor 10mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg alendronic acid, as sodium alendronate

Excipient: Lactose monohydrate.

For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

White, oval shaped tablet embossed "AD10" on one side and "G" on the reverse;

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of osteoporosis in postmenopausal women.
Treatment of osteoporosis in men to reduce the risk of vertebral fractures (see section 5.1)

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

Prophylaxis of glucocorticoid-induced osteoporosis
For post-menopausal women who are not receiving oestrogen treatment the recommended dose is one 10 mg tablet daily.

To permit adequate absorption of alendronate:
Fostepor must be taken at least 30 minutes before the first food, beverage, or medicinal product of the day with plain water only. Other beverages (including mineral water), food and some medicinal products are likely to reduce the absorption of alendronate (see section 4.5).

To facilitate delivery to the stomach and thus reduce the potential for local and oesophageal irritation/adverse experiences (see section 4.4):
• Fostepor should only be swallowed upon arising for the day with a full glass of water (not less than 200 ml or 7 fl.oz.).
• Patients should only swallow Fostepor 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 until after their first food of the day which should be at least 30 minutes after taking the tablet.
• Patients should not lie down for at least 30 minutes after taking Fostepor.
• Fostepor should not be taken at bedtime or before arising for the day.
Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate (see section 4.4).

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

Paediatric patients: Alendronate sodium is not recommended for use in children under the age of 18 years due to insufficient data on safety and efficacy in conditions associated with paediatric osteoporosis (also see section 5.1).

Use in renal impairment: No dosage adjustment is necessary for patients with GFR greater than 35 ml/min. Alendronate is not recommended for patients with renal impairment where GFR is less than 35 ml/min, due to lack of experience.

Fostepor has not been investigated in the treatment of glucocorticoid-induced osteoporosis.

The optimal duration of bisphosphonate treatment for osteoporosis has not been established. The need for continued treatment should be re-evaluated periodically based on the benefits and potential risks of Fostepor 10 mg Tablets on an individual patient basis, particularly after 5 or more years of use.

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 alendronate or to any of the excipients.
• Hypocalcaemia.
• See also section 4.4 .

4.4 Special warnings and precautions for use

Alendronate 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 alendronate is given to patients with active upper gastro-intestinal problems, such as dysphagia, oesophageal disease, gastritis, duodenitis, 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 gastrointestinal tract other than pyloroplasty (see section 4.3).
In patients with known Barrett’s oesophagus, prescribers should consider the benefits and potential risks of alendronate on an individual patient basis.

Oesophageal reactions (sometimes severe and requiring hospitalisation), such as oesophagitis, oesophageal ulcers and oesophageal erosions, rarely followed by oesophageal stricture, have been reported in patients receiving alendronate. Physicians should therefore be alert to any signs or symptoms signalling a possible oesophageal reaction and patients should be instructed to discontinue alendronate and seek medical attention if they develop symptoms of oesophageal irritation such as dysphagia, pain on swallowing or retrosternal pain, new or worsening heartburn.

The risk of severe oesophageal adverse experiences appears to be greater in patients who fail to take alendronate properly and/or who continue to take alendronate 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 section 4.2). Patients should be informed that failure to follow these instructions may increase their risk of oesophageal problems.

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.

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

The following risk factors should be considered when evaluating an individual’s risk of developing osteonecrosis of the jaw:

- potency of the bisphosphonate (highest for zoledronic acid), route of administration (see above) and cumulative dose.
- cancer, chemotherapy, radiotherapy, corticosteroids, smoking.
- a history of dental disease, poor oral hygiene, periodontal disease. invasive dental procedures and poorly fitting dentures.

A dental examination with appropriate preventive dentistry should be considered prior to treatment with oral bisphosphonates in patients with poor dental status.

While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop osteonecrosis of the jaw while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of the jaw. Clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

During bisphosphonate treatment, all patients should be encouraged to maintain good oral hygiene, receive routine dental check-ups, and report any oral symptoms such as dental mobility, pain, or swelling.

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).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 rechallenged with the same drug or another bisphosphonate.

Atypical fractures of the femur
Atypical subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonate therapy, primarily in patients receiving long-term treatment for osteoporosis. These transverse or short oblique, fractures can occur anywhere along the femur from just below the lesser trochanter to just above the supracondylar flare. These fractures occur after minimal or no trauma and some patients experience thigh or groin pain, often associated with imaging features of stress fractures, weeks to months before presenting with a completed femoral fracture. Fractures are often bilateral; therefore the contralateral femur should be examined in bisphosphonate-treated patients who have sustained a femoral shaft fracture. Poor healing of these fractures has also been reported.
Discontinuation of bisphosphonate therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient, based on an individual benefit risk assessment. During bisphosphonate treatment patients should be advised to report any thigh, hip or groin pain and any patient presenting with such symptoms should be evaluated for an incomplete femur fracture.

Patients should be instructed that if they miss a dose of Fostepor, 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 per day, as originally scheduled.
Alendronate is not recommended for patients with renal impairment where GFR is less than 35 ml/min, (see section 4.2).

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

Hypocalcaemia must be corrected before initiating therapy with alendronate (see section 4.3). 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 Fostepor.

Due to the positive effects of alendronate in increasing bone mineral, decreases in serum calcium and phosphate may occur especially in patients taking glucocorticoids in whom calcium absorption may be decreased. These are usually small and asymptomatic. However, there have been rare reports of symptomatic hypocalcaemia, which have occasionally been severe and often occurred in patients with predisposing conditions (e.g. hypoparathyroidism, vitamin D deficiency and calcium malabsorption).

Ensuring adequate calcium and vitamin D intake is 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 medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

If taken at the same time, it is likely that food and beverages (including mineral water), calcium supplements, antacids, and some oral medicinal products will interfere with absorption of alendronate. Therefore, patients must wait at least 30 minutes after taking alendronate before taking any other oral medicinal product (see sections 4.2 and 5.2).
No other interactions with medicinal products of clinical significance are anticipated. A number of patients in the clinical trials received oestrogen (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
Alendronate should not be used during pregnancy. There are no adequate data from the use of alendronate in pregnant women. Alendronate given during pregnancy in rats caused dystocia related to hypocalcaemia. Animal studies revealed effects on foetal bone formation (incomplete ossification) at high doses (see section 5.3).

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

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 Fostepor may affect some patients' ability to drive or operate machinery. Individual responses to Fostepor may vary. (See section 4.8).

4.8 Undesirable effects

In a one-year study in post-menopausal women with osteoporosis the overall safety profiles of Alendronate sodium Once Weekly 70 mg (n=519) and alendronate 10 mg/day (n=370) were similar.
In two three-year studies of virtually identical design, in post-menopausal women (alendronate 10 mg: n=196, placebo: n=397) the overall safety profiles of alendronate 10 mg/day and placebo were similar.
Adverse experiences reported by the investigators as possibly, probably or definitely drug-related are presented below if they occurred in ≥1% in either treatment group in the one-year study, or in ≥1% of patients treated with alendronate 10 mg/day and at a greater incidence than in patients given placebo in the three-year studies:

	One−Year Study		Three−Year Studies	
	‘Fosamax’ Once Weekly 70 mg (n=519) %	alendronate 10 mg/day (n=370) %	alendronate 10 mg/day (n=196) %	Placebo (n=397) %
Gastro-intestinal				
abdominal pain	3.7	3.0	6.6	4.8
Dyspepsia	2.7	2.2	3.6	3.5
acid regurgitation	1.9	2.4	2.0	4.3

Nausea	1.9	2.4	3.6	4.0
abdominal distension	1.0	1.4	1.0	0.8
Constipation	0.8	1.6	3.1	1.8
Diarrhoea	0.6	0.5	3.1	1.8
Dysphagia	0.4	0.5	1.0	0.0
Flatulence	0.4	1.6	2.6	0.5
Gastritis	0.2	1.1	0.5	1.3
gastric ulcer	0.0	1.1	0.0	0.0
oesophageal ulcer	0.0	0.0	1.5	0.0
Musculoskeletal				
musculoskeletal (bone, muscle or joint) pain	2.9	3.2	4.1	2.5
muscle cramp	0.2	1.1	0.0	1.0
Neurological				
Headache	0.4	0.3	2.6	1.5

The following adverse experiences have also been reported during clinical studies and/or post-marketing use: *[Very common (≥1/10), Common (≥1/100, < 1/10), Uncommon (≥1/1000, < 1/100), Rare (≥1/10,000, < 1/1000), Very rare (< 1/10,000)]*

Immune system disorders:	Rare: hypersensitivity reactions including urticaria and angioedema
Metabolism and nutrition disorders:	Rare: symptomatic hypocalcaemia, often in association with predisposing conditions. §
Nervous system disorders:	Common: headache, dizziness† Uncommon: dysgeusia †
Eye disorders:	Uncommon: eye inflammation (uveitis, scleritis, episcleritis)
Ear and labyrinth disorders:	Common: vertigo †
Gastrointestinal disorders:	Common: abdominal pain, dyspepsia, constipation, diarrhoea, flatulence, oesophageal ulcer*, dysphagia*, abdominal distension, acid regurgitation Uncommon: nausea, vomiting, gastritis, oesophagitis*, oesophageal erosions*, melena† Rare: oesophageal stricture*, oropharyngeal ulceration*, upper gastrointestinal PUBs (perforation, ulcers, bleeding) §
Skin and subcutaneous tissue disorders:	Common: alopecia†, pruritus† Uncommon: rash, , erythema Rare: rash with photosensitivity, severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis‡
Musculoskeletal and connective tissue disorders:	Very common: musculoskeletal (bone, muscle or joint) pain which is sometimes severe†§ Common: joint swelling† Rare: Osteonecrosis of the jaw‡§, atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction) ‡§,
General disorders and administration site	Common: asthenia†, peripheral oedema†

conditions:	Uncommon: transient symptoms as in an acute-phase response (myalgia, malaise and rarely, fever), typically in association with initiation of treatment

§ See section 4.4
†Frequency in Clinical Trials was similar in the drug and placebo group.
**See sections 4.2 and 4.4*
‡This adverse reaction was identified through post-marketing surveillance. The frequency of rare was estimated based on relevant clinical trials

4.9 Overdose

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: M 05 BA 04.
Pharmacotherapeutic group: Bisphosphonates. Osteoclast inhibiting agent for the treatment of bone diseases.

Alendronate is a bisphosphonate which in animal studies is deposited below osteoclasts in areas with bone resorption. It inhibits the bone resorption with no direct effect on the bone formation. As both bone resorption and bone formation are linked, the formation of the bone is also reduced, but to a less extent than the resorption, resulting in a progressive increase of the bone mass with normal bone structure. Alendronate is deposited in bone matrix where it is pharmacologically inactive.

In rats the lowest dose of alendronate influencing the bone mineralisation (leading to osteomalacia) was 6000 times higher than the antiresorptive dose. The corresponding relation for etidronate was one to one. These data indicate that alendronate administered in therapeutic doses most probably do not induce osteomalacia.

Osteoporosis in postmenopausal women
Treatment with alendronate in postmenopausal women causes biochemical changes indicating dose-dependent inhibition of the bone resorption. Such biochemical changes returned to the starting point as soon as three weeks after discontinuation of the alendronate therapy despite the long retention of alendronate in the bones.

In studies of up to five years alendronate 10 mg/day reduced the biochemical markers for bone resorption during three to six months by approximately 50-70% to a level corresponding to the level in healthy, premenopausal women. Likewise, the markers for bone formation were reduced by 25-50% after six to twelve months. The new level of bone resorption and bone formation was maintained for the rest of the alendronate treatment period.

Effect on bone mineralisation density
In clinical trials alendronate 10 mg once daily for three years resulted in increased bone mineralisation density (BMD) in postmenopausal women with osteoporosis. Following treatment for three years with alendronate 10 mg/day the BMD increase (versus placebo) was approximately 8.8% in columna lumbalis, 5.9% in collum femoris, 7.8% in trochanter, 2.25 in the forearm and 2.5% in the whole body. In the two-year prolongation of these trials, treatment with alendronate 10 mg/day resulted in further increase of BMD in columna spinals and trochanter (absolute further increase between year 3 and 5: Columnia spinalis 0.94%, trochanter 0.88%). BMD in collum femoris, in the forearm and in the whole body remained the same.

The effect of alendronate was the same regardless of age, race, initial bone metabolism rate, renal function and use together with a wide range of other drugs.

Following discontinuation of alendronate after 1-2 years of treatment, neither a further increase of the bone mass, nor an accelerated bone loss were observed. These data indicate that daily treatment with Fostepor must continue to obtain a progressive increase of the bone mass.

Effect on fracture incidence
Alendronate gives the same reduction of incidence of both vertebral and non-vertebral fractures in patients who have not had fractures and in patients who had previous had a vertebral fracture.

The following results were reported from an analysis of pooled three-year data from the two main treatment trials with varying doses of alendronate to postmenopausal women: 48% reduction of the number of patients developing one or more vertebral fractures (alendronate 3.2% versus placebo 6.2%). In patients who developed vertebral fractures, the loss of height was smaller in those treated with alendronate (5.9 mm versus 23.3 mm). Pooled data from five trials of 2-3 years duration showed a 29% reduction in the number of non-vertebral fractures (alendronate 9.0% versus placebo 12.6%).

Three years of treatment with alendronate (5 mg/day for the first two years and 10 mg/day in the third year) in menopausal women with osteoporosis (who have had at least one vertebral compression fracture) resulted in a reduction of the following fracture incidences: The proportion of patients who experienced at least one new vertebral fracture (alendronate 8.0% versus placebo 15.0% - a reduction of 47%); patients with at least two new vertebral fractures (0.5% versus 4.9% – a reduction of 90%); any clinical (i.e. painful) fracture (13.7% versus 18.3% - a reduction of 28%; hip fracture (1.1% versus 2.2% - a reduction of 51%); wrist (forearm) fracture (2.2% versus 4.1% - a reduction of 48%).

Bone histology
The bone histology in 270 postmenopausal patients with osteoporosis treated with alendronate in a dosage of 1-20 mg/day for 1-3 years, showed normal mineralisation and structure as well as an expected reduction in the bone metabolism as compared with placebo. Long-term treatment with alendronate in rats and baboons showed normal bone histology and increased bone strength.

Co-therapy with oestrogen/hormone substitution (HRT):
The effect on BMD of alendronate 10 mg once daily and conjugated oestrogen (0.625 mg/day) either alone or in combination was assessed in a two-year study of postmenopausal women with osteoporosis and hysterectomy. After two years the increase in columna lumbalis BMD from base line was significantly larger with the combination (8.3%) than with either oestrogen or alendronate treatment alone (both 6%).

The effect on BMD when alendronate was added to long-term therapy (at least one year) with HRT (oestrogen +/- gestagen) was assessed in a one-year study of postmenopausal women with osteoporosis. The addition of alendronate 10 mg at least once daily to HRT after one year resulted in a significant larger increase of columna lumbalis BMD (3.7%) compared with HRT alone (1.1%).

These studies showed a significantly more favourable trend in BMD with combined treatment than with HRT alone, for the whole hip, collum femoris and trochanter. The study showed no significant effect on the overall body BMD.

Treatment of osteoporosis in men
The efficacy of alendronate in men with osteoporosis was demonstrated in a clinical trial.

In a two years study 10 mg of alendronate was administered once daily to men (age group 31 to 87 years, average 66 years). After two years the average significant increase in BMD compared to treatment with placebo was the following: columna lumbalis, 5.3%; collum femoris, 2.6%; trochanter, 3.1% and total BDM 1.6%.

In 127 men receiving 10 mg alendronate the incidence of new vertebral fractures (measured with quantitative radiography) was reduced significantly when compared with placebo (0.8% versus 7.1% respectively) and similarly

reduced the lowering of height (-0.6 versus 2.4 mm -respectively). This is in line with other essential larger studies in post menopausal women.

There is no documented reduction of the incidence of clinical fractures in vertebrae.
There is no documented reduction of the incidence of non-vertebral fractures in men.

Paediatric patients
Alendronate sodium has been studied in a small number of patients with osteogenesis imperfecta under the age of 18 years. Results are insufficient to support the use of alendronate sodium in paediatric patients with osteogenesis imperfecta.

Laboratory test findings
In clinical studies, asymptomatic, mild and transient decreases in serum calcium and phosphate were observed in approximately 18 and 10%, respectively, of patients taking alendronate 10 mg/day versus approximately 12 and 3% of those taking placebo. However, the incidences of decreases in serum calcium to <8.0 mg/dl (2.0 mmol/l) and serum phosphate to ≤2.0 mg/dl (0.65 mmol/l) were similar in both treatment groups.

5.2 Pharmacokinetic properties

Absorption:
Oral bioavailability for alendronate in women is 0.7% for doses from 5-40 mg when administered on an empty stomach and two hours prior to a standard breakfast. Oral bioavailability in men (0.6%) was approximately the same as in women. Bioavailability was reduced with approximately 40% when alendronate was given half to one hour before a standard breakfast.
Bioavailability was negligible regardless of whether alendronate was taken with or up to two hours after a standard breakfast. Coffee and orange juice reduce bioavailability with approximately 60% (See Section 4.2 Posology and method of administration).

In healthy volunteers oral prednisone (20 mg thrice daily for five days) did not change the bioavailability of alendronate significantly (average increase from 20-44%).

Distribution:
Protein binding is approximately 78%. Preclinical studies show a distribution of alendronate to soft tissue and then a fast redistribution to the bones where it is bound or excreted with urine. Steady state distribution volume in the body's soft tissue is at least 28 litres (22-35 litres). The plasma concentrations of the medicinal product following administration of an oral therapeutic dose is below detection limit (<5 ng/ml).

Biotransformation:
Alendronate has no known metabolites.

Elimination:
Approximately 50% of ^{14}C labelled alendronate is excreted via urine within 72 hours. Very little or no radioactivity is recovered in faeces. The rest is deposited in bone tissue where it is inactive. Renal clearance is 71 ml/minute after a single dose of 10 mg IV. Within six hours the plasma concentration declines with more than 95% following IV administration. Then alendronate is slowly released from the skeleton. Estimated half life is thus >10 years.

Patient characteristics:
Preclinical investigations show that the medicinal product which is not deposited in the bone, is excreted fast in the urine. Following chronic dosage of cumulative IV doses of up to 35 mg/kg in animals no saturation of bone uptake has been demonstrated. In animals the elimination of alendronate via the kidneys is reduced with reduced renal function. No corresponding information is available for human beings, but a larger accumulation of alendronate in bones must be expected in humans in case of reduced renal function (see Section 4.2 Dosage).

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeat dose

toxicity, genotoxicity and carcinogenic potential. Studies in rats have shown that treatment with alendronate during pregnancy was associated with dystocia in dams during parturition which was related to hypocalcaemia. In studies, rats given high doses showed an increased incidence of incomplete foetal ossification. The relevance to humans is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose (E460).
Lactose monohydrate.
Croscarmellose sodium.
Magnesium stearate (E572).
Povidone.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Keep in the original package. No special precaution for storage.

6.5 Nature and contents of container

Green opaque aluminium/PVC blister packs.

Polypropylene container with polyethylene cap.

Pack sizes:
Blisters: 10, 14, 28, 30 and 98 tablets*
Containers: 28, 30, 50, 98, 100, 112 and 250 tablets*
*Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

McDermott Laboratories Ltd. t/a Gerard Laboratories
35/36 Baldoyle Industrial Estate, Grange Road,
Dublin 13

8 MARKETING AUTHORISATION NUMBER

PA 577/86/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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