SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Alendronic Acid and Calcium Cholecalciferol 70 mg + 1000 mg / 880 IU film-coated tablets + effervescent tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet contains 70 mg of alendronic acid (as 91.35 mg sodium alendronate trihydrate).

One effervescent tablet contains 2500 mg of calcium carbonate (equivalent to 1000 mg calcium) and 22 micrograms (880 IU) of cholecalciferol (vitamin D3).

Excipient(s) with known effect: One effervescent tablet contains 376.2 mg of lactose, 4.2 mmol (96 mg) of sodium, sucrose and soya oil.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet
White, round, biconvex film-coated tablet (diameter 10 mm), debossed with "ALN 70" on one side.

Effervescent tablet
White, round, biplane effervescent tablet (diameter 30 mm) with the odour of orange.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of post-menopausal osteoporosis. Alendronate reduces the risk of vertebral and hip fractures.

Alendronic Acid Tablets + Calcium Cholecalciferol Effervescent Tablets is only intended for use in assessed patients for whom the amount of calcium and vitamin D3 included is considered to provide adequate supplementation.

4.2 Posology and method of administration

Alendronic Acid Tablets + Calcium Cholecalciferol Effervescent Tablets is a weekly therapy of 1 Alendronate 70 mg film-coated tablet and 6 calcium/vitamin D3 effervescent tablets.

The recommended dose is one Alendronate 70 mg film-coated tablet on the first day followed on the next day by 1 calcium/vitamin D3 effervescent tablet daily for 6 days. This 7-day sequence is then repeated each week starting with Alendronate 70 mg film-coated tablet.

Alendronate 70 mg (film-coated tablet)
Posology
The Alendronate 70 mg film-coated tablet should be taken orally on the same day each week.

The recommended dose is one 70 mg tablet once weekly. 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 Alendronate 70 mg film-coated tablet on an individual patient basis, particularly after 5 or more years of use.

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.

Use in renal impairement
No dose adjustment is necessary for patients with a glomerular filtration rate (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 the lack of experience.

Use in impaired hepatic function
No dose adjustment is necessary.

Paediatric population
Alendronate 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)..

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

Method of administration

To permit adequate absorption of alendronate

Alendronic Acid Tablets + Calcium Cholecalciferol Effervescent Tablets must be taken on an empty stomach immediately on rising in the morning, with plain water only, at least 30 minutes before the first food, drink or other medicinal product of the day. Other drinks (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/side effects (see section 4.4).

- Alendronic Acid Tablets + Calcium Cholecalciferol Effervescent Tablets 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 swallow Alendronic Acid Tablets + Calcium Cholecalciferol Effervescent Tablets whole. Patients should not crush or chew, or allow the tablet to dissolve in their mouth because of the 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 Alendronic Acid Tablets + Calcium Cholecalciferol Effervescent Tablets.

Alendronic Acid Tablets + Calcium Cholecalciferol Effervescent Tablets should not be taken at bedtime or before arising for the day.

<u>Calcium/vitamin D3 (effervescent tablet)</u>

<u>Posology</u>

Calcium/vitamin D3 effervescent tablet should be taken each day for 6 days per week starting on the day after the Alendronate 70 mg film-coated tablet is taken.

In case the Alendronate 70 mg film-coated tablet dose is missed, patients should be instructed that the Alendronate 70 mg film-coated tablet should be taken on the next day in the morning according to the dosing instructions. In this particular instance, patients should then take their calcium/vitamin D3 effervescent tablet on the following day. Patients should be instructed that they should never take the film-coated tablet and the effervescent tablet the same day.

If the calcium/vitamin D3 effervescent tablet dose is missed, the patient should be instructed to continue taking one effervescent tablet each day beginning on the day the missed dose is remembered. Patient should be instructed that they should not take two effervescent tablets on the same day. Any remaining calcium/vitamin D3 effervescent tablet at the end of the weekly cycle should be discarded.

Paediatric population

Calcium/vitamin D3 is not intended for intake in children.

Method of administration
The effervescent tablet is taken dissolved in a glass of water.

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, calcium carbonate, cholecalciferol, soya, peanut or to any of the excipients listed in section 6.1.
- Hypocalcaemia
- Hypercalcaemia
- Hypercalciuria
- Diseases and/or conditions (such as prolonged immobilization) associated with hypercalcaemia and/or hypercalciuria
- Nephrolithiasis, nephrocalcinosis
- Hypervitaminosis D
- Severe renal impairment

See also section 4.4.

4.4 Special warnings and precautions for use

Alendronate
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 a major gastro-intestinal disease such as peptic ulcer, or active gastrointestinal bleeding, or surgery of the upper gastro-intestinal 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. The physician 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 side effects 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 rarer (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 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 sugery 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.

Osteonecrosis of the external auditory canal has been reported with bisphosphonates, mainly in association with long-term therapy. Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma. The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving bisphosphonates who present with ear symptoms including chronic ear infections.

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 medicinal product or another bisphosphonate.

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.

In post-marketing experience, there have been rare reports of severe skin reactions including Stevens Johnson syndrome and toxic epidermal necrolysis.

Patients should be instructed that if they miss a dose of Alendronic Acid Tablets + Calcium Cholecalciferol Effervescent Tablets they should take one film-coated tablet on the morning after they remember. They should not take two film-coated tablets on the same day, but should return to taking one film-coated tablet a week, as originally scheduled on their chosen day.

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 before starting alendronate. In patients with these conditions serum calcium and symptoms of hypocalcaemia should be monitored during therapy with alendronate.

Due to the positive effects of alendronate in increasing bone mineral, decrease in serum calcium and serum 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.

Calcium /vitamin D3
Calcium/Vitamin D3 should be used with caution in patients with hypercalcaemia or signs of impaired renal function and the effect on calcium and phosphate levels should be monitored. The risk of soft tissue calcification should be taken into account. In patients with severe renal insufficiency, vitamin D in the form of cholecalciferol is not metabolised normally and another form of vitamin D should be used (see section 4.3)

During long-term treatment, serum and urinary calcium levels should be followed and renal function should be monitored through measurement of serum creatinine. Monitoring is especially important in elderly patients on concomitant treatment with cardiac glycosides or diuretics (see section 4.5) and in patients with a high tendency to calculus formation. Treatment must be reduced or suspended if urinary calcium exceeds 7.5 mmol/24 hour (300 mg/24 hour). In case of hypercalcaemia or signs of impaired renal function, treatment with calcium/vitamin D3 effervescent tablets should be discontinued.

The dose of vitamin D3 in the effervescent tablets should be considered when prescribing other medicinal products containing vitamin D. Additional doses of calcium or vitamin D should be taken under close medical supervision. In such cases it is necessary to monitor serum calcium levels and urinary calcium excretion frequently.

Calcium carbonate/vitamin D3 effervescent tablets should be used with caution in patients suffering from sarcoidosis because of the risk of increased metabolism of vitamin D to its active metabolite. In these patients, serum calcium levels and urinary calcium excretion must be monitored.

Calcium carbonate/vitamin D3 effervescent tablets should be used with caution in immobilised patients with osteoporosis due to the increased risk of hypercalcaemia. The calcium/vitamin D3 treatment might be discontinued in prolonged immobilization and should only be resumed once the patient becomes mobile again.

Excipients
The Calcium carbonate/vitamin D3 effervescent tablets contain lactose and sucrose. Patients with rare hereditary problems of galactose intolerance, fructose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicinal product.

The Calcium carbonate/vitamin D3 effervescent tablets contain 96 mg sodium per tablet.

The alendronate film-coated tablets contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Alendronate

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 undesirable effects 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.

Calcium carbonate/vitamin D3

Thiazide diuretics reduce the urinary excretion of calcium. Due to increased risk of hypercalcemia serum calcium should be regularly monitored during concomitant use of thiazide diuretics.

Systemic corticosteroids reduce calcium absorption. During concomitant use, it may be necessary to increase the dose of calcium.

Calcium carbonate may interfere with the absorption of concomitant administered tetracycline preparations. For this reason, tetracycline preparations should be administered at least two hours before or four to six hours after oral intake of calcium carbonate/vitamin D3.

Hypercalcaemia may increase the toxicity of digitalis and other cardiac glycosides (risk of dysrhythmia) during treatment with calcium combined with vitamin D3. Such patients should be monitored with regard to electrocardiogram (ECG) and serum calcium levels.

If sodium fluoride is used concomitantly, this preparation should be administered at least three hours before intake of calcium carbonate/vitamin D3 since gastrointestinal absorption may be reduced.

Oxalic acid (found in spinach and rhubarb) and phytic acid (found in whole cereals) may inhibit calcium absorption through formation of insoluble compounds with calcium ions. The patient should not take calcium products within two hours of eating foods with high concentration of oxalic acid and phytic acid.

Simultaneous treatment with ion exchange resins such as cholestyramine or laxatives such as paraffin oil may reduce the gastrointestinal absorption of vitamin D.

4.6 Fertility, pregnancy and lactation

Alendronic Acid Tablets + Calcium Cholecalciferol Effervescent Tablets is only intended for use in postmenopausal women and therefore it should not be used during pregnancy or in breast-feeding women.

Pregnancy
Alendronate
There are no or limited amount of data from the use of alendronate in pregnant women. Studies in animals have shown reproductive toxicity. Alendronate given during pregnancy in rats caused dystocia related to hypocalcemia (see section 5.3).

Alendronate should not be used during pregnancy.

Calcium carbonate/vitamin D3
During pregnancy the daily intake should not exceed 1500 mg calcium and 600 IU cholecalciferol (15µg vitamin D3). Studies in animals have shown reproductive toxicity with high doses of vitamin D. On account of the high vitamin D dose, calcium/colecalciferol should not be used during pregnancy.

Breastfeeding
Alendronate
It is not known whether alendronate/metabolites are excreted into human breast milk. A risk to the newborns/infants cannot be excluded. Alendronate should not be used during breast-feeding.

Calcium carbonate/vitamin D3
Calcium and vitamin D 3 pass into breast milk.

Fertility
Alendronate
Bisphosphonates are incorporated into the bone matrix, from which they are gradually released over a period of years. The amount of bisphosphonate incorporated into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the dose and duration of bisphosphonate use (see section 5.2). There are no data on fetal risk in humans. However, there is a theoretical risk of fetal harm, predominantly skeletal, if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of

bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on the risk has not been studied.

Calcium carbonate/vitamin D3
Normal endogenous levels of calcium and vitamin D are not expected to have any adverse effects on fertility.

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

Calcium/vitamin D3 have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Alendronate

In a one-year study in post-menopausal women with osteoporosis the overall safety profiles for alendronate once-weekly tablets (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 daily and placebo were similar.

Undesirable effects 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 the patients treated with alendronate 10 mg per day and at a incidence higher than in patients given placebo in the three-year studies:

	The one-year study		Three-year studies	
	Alendronate 70 mg once-weekly tablet (n=519) %	Alendronate 10 mg daily (n=370) %	Alendronate 10 mg daily (n=196) %	Placebo (n=397) %
Gastrointestinal				
Abdominal pain	3.7	3.0	6.6	4.8
Dyspepsia	2.7	2.2	3.6	3.5

	The one-year study		Three-year studies	
	Alendronate 70 mg once-weekly tablet (n=519) %	Alendronate 10 mg daily (n=370) %	Alendronate 10 mg daily (n=196) %	Placebo (n=397) %
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 pain (bone, muscle or joints)	2.9	3.2	4.1	2.5
Muscle cramps	0.2	1.1	0.0	1.0
Neurological				
Headache	0.4	0.3	2.6	1.5

The following undesirable effects have also been reported in clinical trials and/or post marketing:

MedDRA frequency convention
Very common (≥ 1/10)
Common (≥ 1/100 to < 1/10)
Uncommon (≥ 1/1,000 to < 1/100)
Rare (≥ 1/10,000 to < 1/1,000)
Very rare (< 1/10,000)
Not known (cannot be estimated from the available data)

MedDRA-system organ class	Very common	Common	Uncommon	Rare	Very rare	Not known
Immunesystem disorders				Hypersensitivity reactions including urticaria and angioedema		

MedDRA-system organ class	Very common	Common	Uncommon	Rare	Very rare	Not known
Metabolism and nutrition disorders				Symptomatic hypocalcaemia, generally in connection with predisposing conditions[§]		
Nervous system disorders		Headache, dizziness[†]	Dysgeusia[†]			
Eye disorders			Uveitis, scleritis, episcleritis			
Ear and labyrinth disorders		Vertigo[†]				
Gastrointestinal disorders		Abdominal pain, dyspepsia, constipation, diarrhoea, flatulence, oesophageal ulcer[*], dysphagia[*], abdominal distension, acid regurgitation	Nausea, vomiting, gastritis, oesophagitis[*], oesophageal erosions[*], melaena[†]	Oesophageal stricture[*], oropharyngeal ulceration[*], upper gastrointestinal PUBs (perforation, ulcer, bleeding)[§]		
Skin and subcutaneous tissue disorders		Alopecia[†], pruritus[†]	Rash, erythema	Rash with photosensitivity, severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis[‡]		
Musculoskeletal and connective tissue disorders	Musculoskeletal (bone, muscle or joint) pain which is sometimes severe[†§]	Joint swelling[†]		Osteonecrosis of the jaw[‡§], atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction)[‡§]	Osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction)	

MedDRA-system organ class	Very common	Common	Uncommon	Rare	Very rare	Not known
General disorders and administration site conditions		Asthenia[†], peripheral oedema[†]	Transient symptoms as in an acute phase reaction (myalgia, malaise and in rare cases fever) usually in connection with the start of treatment[†]			

[§]See section 4.4
[†]Frequency in clinical trials was similar in the medicinal product 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
[1]Identified in postmarketing experience.

Osteonecrosis of the jaw
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 osteomyelistis). Diagnosis of cancer, chemotherapy, radiotherapy, corticosteroids and poor oral hygiene are also deemed as risk factors; severe musculoskeletal (bone, muscle or joint) pain (see section 4.4).

Calcium carbonate/vitamin D3

MedDRA-system organ class	Very common	Common	Uncommon	Rare	Very rare	Not known
Immune system disorders				Hypersensitivity reactions	Isolated cases of systemic allergic reactions (anaphylactic reaction, face oedema, laryngeal oedema, angioneurotic oedema) have been reported.	

MedDRA-system organ class	Very common	Common	Uncommon	Rare	Very rare	Not known
Metabolism and nutrition disorders			Hypercalcaemia and hypercalciuria		Milk-alkali syndrome (frequent urge to urinate, continuing headache, continuing loss of appetite, nausea or vomiting, unusual tiredness or weakness, hypercalcaemia, alkalosis and renal impairment). Seen usually only in overdose (see section 4.9).	
Gastrointestinal disorders				Constipation, flatulence, nausea, vomiting, abdominal pain and diarrhoea		
Skin and subcutaneous disorders				Pruritus, skin rash and urticaria		

Special patient group
Renal impairment
Patients with renal impairment are at increased risk for hyperphosphataemia, nephrolithiasis and nephrocalcinosis (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via the yellow Card Scheme: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in Google play or Apple App store.

4.9 Overdose

Alendronate
Symptoms

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

Management
There is no specific information available on the treatment of overdosage with alendronate. Milk or antacids should be given in order to bind alendronate. On account of the risk of oesophageal irritation, vomiting should not be induced and the patient should be kept in an upright position.

Calcium carbonate/vitamin D3
Symptoms
Overdose can lead to hypervitaminosis, hypercalciura and hypercalcaemia. Symptoms of hypercalcaemia may include anorexia, thirst, nausea, vomiting, constipation, abdominal pain, muscle weakness, fatigue, mental disturbances, polydipsia, polyuria, bone pain, nephrocalcinosis, renal calculi and in severe cases, cardiac arrhythmias. Extreme hypercalcaemia may result in coma and death. Persistently high calcium levels may lead to irreversible renal damage and soft tissue calcification.

Treatment of hypercalcaemia
Treatment is essentially symptomatic and supportive. The treatment with calcium/vitamin D3 effervescent tablets must be discontinued. Treatment with thiazide diuretics, lithium, vitamin A, vitamin D3 and cardiac glycosides must also be discontinued (see section 4.5).

Emptying of the stomach in patients with impaired consciousness.
Rehydration, and, according to severity, isolated or combined treatment with loop diuretics, bisphosphonates, calcitonin and corticosteroids. Serum electrolytes, renal function and diuresis must be monitored. In severe cases, ECG and central venous pressure should be followed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Drugs affecting bone structure and mineralisation, Bisphosphonates, combinations
ATC Code: M05BB05

Alendronate
The active substance in Alendronic Acid Tablets + Calcium Cholecalciferol Effervescent Tablets, sodium alendronate trihydrate, is a bisphosphonate that inhibits osteoclastic bone resorption without any direct effect on bone formation. Preclinical studies have demonstrated a preference for localisation of alendronate to sites where active resorption takes place. Osteoclastic

activity is inhibited but formation and binding of the osteoclasts is not affected. Bone formed during treatment with alendronate is of normal quality.

Treatment of post-menopausal osteoporosis
Osteoporosis is defined as bone mineral density (BMD) of the spine or hip 2.5 standard deviations below the mean value of a normal young population or as a previous fragility fracture, irrespective of BMD.

The therapeutic equivalence of alendronate once-weekly tablets (n=519) and alendronate 10 mg daily (n=370) was demonstrated in a one-year multicentre study in post-menopausal women with osteoporosis. The mean increase from baseline of BMD in the lumbar spine after one year was 5.1 % (95 % confidence interval: 4.8, 5.4 %) in the group receiving 70 mg once per week and 5.4 % (95 % confidence interval: 5.0, 5.8 %) in the group receiving 10 mg daily. The average increases in BMD in the group receiving 70 mg once per week and in the group receiving 10 mg daily were 2.3 % and 2.9 % in the femoral neck and 2.9 % and 3.1 % over the total hip. The two treatment groups were also similar with regard to increased bone density in other parts of the skeleton.

The effects of alendronate on BMD and fracture incidence in post-menopausal women were studied in two initial efficacy studies of identical design (n=994), and in the *Fracture Intervention Trial* (FIT: n=6459).

In the initial efficacy studies, the increases in BMD with alendronate 10 mg daily relative to placebo after three years were 8.8 %, 5.9 % and 7.8 % at the spine, femoral neck and trochanter respectively. Total body BMD also increased significantly. In the patients treated with alendronate, the proportion of patients who suffered one or more vertebral fractures was reduced by 48 % (alendronate 3.2 % versus placebo 6.2 %). In the two-year extensions of these studies the BMD in the spine and trochanter continued to increase. In addition, BMD at the femoral neck and total body was maintained.

The FIT study included two placebo-controlled trials in which alendronate was given daily (5 mg daily for two years and 10 mg daily for a further one or two years).

- FIT 1: A three-year study with 2027 patients who had had at least one baseline vertebral (compression) fracture. In this study alendronate daily reduced the incidence of ≥ 1 new vertebral fracture by 47 % (alendronate 7.9 % versus placebo 15.0 %). In addition, a statistically significant reduction in the incidence of hip fractures was confirmed (1.1 % versus 2.2 %, a reduction of 51 %).
- FIT 2: A four-year study with 4432 patients who had a low bone mass but had not had any vertebral fracture at the start of the study. In this study, in a subgroup analysis of osteoporotic women (37 % of the total population who fulfilled the definition of osteoporosis given above) a significant difference was seen in the incidence of hip fractures (alendronate 1.0 % versus placebo 2.2 %, a reduction of 56 %) and in the incidence of ≥1 vertebral fracture (2.9 % versus 5.8 %, a reduction of 50 %).

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.

Paediatric population
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.

Calcium carbonate/vitamin D3
In case of calcium deficiency, oral intake of calcium supplementation supports the remineralisation of the skeleton. Vitamin D3 increases the intestinal absorption of calcium.

Administration of calcium and vitamin D3 counteracts the increase in parathyroid hormone (PTH) which is caused by calcium deficiency which causes increased bone resorption.

A clinical study of institutionalised patients suffering from vitamin D deficiency indicated that a daily intake of effervescent granules of 1000 mg calcium/880 IU cholecalciferol for six months normalised the value of the 25-hydoxylated metabolite of vitamin D3 and reduced secondary hyperparathyroidism.

5.2 Pharmacokinetic properties

Alendronate
Absorption
Compared with an intravenous reference dose, the mean oral bioavailability of alendronate in women was 0.64 % for doses ranging from 5 to 70 mg given after an overnight fast and two hours before a standardised breakfast. Bioavailability decreased to an estimated 0.46 % and 0.39 % when alendronate was given an hour or half an hour before a standardised breakfast. In osteoporosis studies alendronate was effective when it was given at least 30 minutes before the first meal or drink of the day.

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

In healthy persons, oral prednisolone (20 mg three times daily for five days) did not result in any clinically meaningful change in the oral bioavailability of alendronate (a mean increase ranging from 20 % to 44 %).

Distribution
Studies in rats show that alendronate is initially distributed to soft tissues after intravenous administration of 1 mg/kg, but is then rapidly redistributed to the skeleton or excreted in the urine. The mean steady-state volume of distribution, exclusive of bone, is at least 28 litres in humans. Concentrations of alendronate 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 intravenous 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 intravenous dose of 10 mg, 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 intravenous 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 thought to interfere with the excretion of other medicinal products by those systems in humans.

Renal impairment
Non clinical studies show that the amount of medicinal product not deposited in bone is rapidly excreted in the urine. No evidence of saturation of bone uptake was found after chronic dosing with cumulative intravenous 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).

<u>Calcium carbonate</u>
Absorption
During dissolution the calcium salt contained in the effervescent granules is transformed into calcium citrate. Calcium citrate is well absorbed, approximately 30% to 40% of the ingested dose.

Distribution and biotransformation
99% of calcium in the body is concentrated in the hard structure of bones and teeth. The remaining 1% is present in the intra- and extracellular fluids. About 50% of the total blood calcium content is physiologically active ionised form

with approximately 10% being complexed to citrate, phosphate or other anions, the remaining 40% being bound to proteins, principally albumin.

Elimination
Calcium is eliminated through faeces, urine and sweat. Renal excretion depends on glomerular filtration and calcium tubular reabsorption.

Vitamin D3
Absorption
Vitamin D is readily absorbed in the small intestine.

Distribution and biotransformation
Cholecalciferol and its metabolites circulate in the blood bound to a specific globulin. Cholecalciferol is converted in the liver by hydroxylation to the active form 25-hydroxycholecalciferol. It is then further converted in the kidneys to 1,25 hydroxycholecalciferol. 1,25 hydroxycholecalciferol is the metabolite responsible for increasing calcium absorption. Vitamin D that is not metabolised is stored in adipose and muscle tissues.

Elimination
Vitamin D is excreted in faeces and urine.

5.3 Preclinical safety data

Alendronate
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. Studies in female rats showed that treatment with alendronate during pregnancy was associated with dystocia during parturition, which was related to hypocalcaemia. Studies in which rats were given high doses showed an increased incidence of incomplete foetal bone formation. The relevance for humans is unknown.

Calcium carbonate/vitamin D3
At doses far higher than the human therapeutic range, teratogenicity has been observed in animal studies (see section 4.6). There is no further information of relevance to the safety assessment in addition to what is stated in other parts of the SmPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Film-coated tablet
Tablet core
Cellulose, microcrystalline
Anhydrous silica, colloidal
Croscarmellose sodium
Magnesium stearate

Tablet coating
Cellulose, microcrystalline
Carrageenan
Macrogol 8000
Effervescent tablet
Citric acid, anhydrous
Simeticone
Gelatin
Lactose monohydrate
Macrogol 6000
Maize starch
Methylcellulose
Sodium cyclamate
Sodium hydrogen carbonate
Povidone K25
Saccharin sodium
Soya-bean oil, hydrogenated
Sucrose
Alpha-tocopherol
Orange juice flavour (PHS-133147)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

Effervescent tablets
Shelf life after first opening: 1 month

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

The film-coated tablets are packed in
OPA-Aluminium-PVC/Aluminium blister.

The effervescent tablets are packed in
Polypropylene tubes with polyethylene stopper containing a silica gel desiccant.

Pack sizes
1 film-coated tablet + 6 effervescent tablets
2 film-coated tablets + 12 effervescent tablets
4 film-coated tablets + 24 (2 x 12) effervescent tablets
3 x (4 film-coated tablets + 24 (2 x 12) effervescent tablets)
4 x (4 film-coated tablets + 24 (2 x 12) effervescent tablets)
6 x (4 film-coated tablets + 24 (2 x 12) effervescent tablets)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Sandoz Limited
Park View, Riverside Way
Watchmoor Park
Camberley, Surrey
GU15 3YL
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 04416/1163

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/03/2013

10 DATE OF REVISION OF THE TEXT

08/08/2020