SUMMARY OF THE PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Tridepos 70 mg + 500 mg/800 IU tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Tridepos is a combination pack of two tablets: Alendronate 70 mg tablets and calcium/cholecalciferol 500 mg/800 IU tablets.

Alendronate tablets: Each tablet contains sodium alendronate trihydrate equivalent to 70 mg alendronic acid.

Calcium/cholecalciferol tablets: Each tablet contains calcium carbonate equivalent to 500 mg calcium and cholecalciferol (vitamin D_3) 800 IU (20 microgram).

Excipient(s) with known effect:
Alendronate tablet: Each tablet contains lactose 122 mg (as monohydrate).
Calcium/cholecalciferol tablets: Each tablet contains sucrose 1.75 mg.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Alendronate
Tablet.
White, oblong, biconvex, 5.5 x 11.5 mm.

Calcium/cholecalciferol
Film-coated tablet
White to off-white, dots may occur, oval, engraved R150, 8.5 x 19 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Tridepos is indicated for the treatment of postmenopausal osteoporosis, to reduce the risk of vertebral and hip fractures. Tridepos is intended for use in patients who are at risk of calcium and vitamin D deficiency.

4.2 Posology and method of administration

Each blister contains 1 tablet of Alendronate 70 mg and 6 tablets of calcium/cholecalciferol 500 mg/800 IU covering 1 week of treatment.

Posology
One tablet Alendronate 70 mg and 6 tablets of calcium/cholecalciferol 500 mg/800 IU per week, to be taken on consecutive days of the week.
Treatment should be started with Alendronate 70 mg on Day 1 of treatment (= chosen by the patient at the start of treatment), followed by one calcium/cholecalciferol 500 mg/800 IU tablet daily on 6 consecutive days (day 2 to day 7).

The day after taking the sixth calcium/cholecalciferol tablet (= Day 8), the 7-day treatment sequence is repeated, starting with a tablet Alendronate 70 mg.

In case the Alendronate tablet dose is missed, patients should be instructed that the Alendronate tablet should be taken on the next day in the morning according to the dosing instructions. The calcium/cholecalciferol tablet must be taken at least 30 minutes after the Alendronate since calcium interferes with the absorption of alendronate.

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

The optimal duration of bisphosphonate treatment for osteoporosis has not been established. The need for continued treatment should be re-assessed periodically based on the benefits and potential risks of alendronate for the individual patient, especially after 5 years of use or more.

The amount of calcium in the calcium/cholecalciferol tablets is lower than the recommended daily intake. Therefore, the patient's dietary intake of calcium should be estimated by the prescriber and Tridepos is mainly intended for use by patients with a dietary intake of calcium of 500 mg-1000 mg per day.

Tridepos is a combination product with once-daily dosing which facilitates the sequential administration of alendronate and calcium/ cholecalciferol.

Use in the elderly

In clinical studies there was no age-related difference in the efficacy or safety profiles of alendronate. However, renal function of the elderly patient should be taken into account (see section 4.4).

Use in renal impairment

Tridepos should be used with caution in patients with impairment of renal function and the effect on calcium and phosphate levels should be monitored. Tridepos is contraindicated in severe renal insufficiency (see section 4.3).

Paediatric population

Tridepos is not recommended for use in children.

Method of administration

Alendronate 70 mg
To permit adequate absorption of alendronate, Alendronate 70 mg 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.)

- Alendronate tablets should only be swallowed upon arising for the day with a full glass of water (not less than 200 ml)

- Patients should only swallow Alendronate tablets 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 Alendronate tablets.
- Alendronate tablets should not be taken at bedtime or before arising for the day.

Calcium/cholecalciferol
To be swallowed with water, whole, crushed or divided.

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
- Severe renal impairment
- Hypocalcaemia
- Diseases and/or conditions resulting in hypercalcaemia and/or hypercalciuria
- Nephrolithiasis
- Hypervitaminosis D
- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

See also section 4.4

4.4 Special warnings and precautions for use

Gastro intestinal adverse events
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 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. 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.

Renal function
Alendronate is not recommended for patients with renal impairment where GFR is less than 35 ml/min (see section 4.2).
Vitamin D should be used with caution in patients with impairment of 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 other forms of vitamin D should be used (see section 4.3).
During long-term treatment, serum calcium levels should be followed and renal function should be monitored through measurements 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. In case of hypercalcaemia or hypercalciuria (exceeding 300 mg (7.5 mmol)/24 hours) or signs of impaired renal function the treatment with Tridepos should be discontinued.

Calcium levels
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 treated. In patients with these conditions, serum calcium and symptoms of hypocalcaemia should be monitored during therapy with Tridepos.

Due to the 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.

Calcium/cholecalciferol tablets should be prescribed with caution to patients suffering from sarcoidosis due to risk of increased metabolism of vitamin D into its active form. These patients should be monitored with regard to the calcium content in serum and urine.

Calcium/cholecalciferol tablets should be used cautiously in immobilised patients with osteoporosis due to increased risk of hypercalcaemia.

The content of vitamin D (800 IU) in calcium/cholecalciferol 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.

Osteonecrosis of the jaw and external auditory canal
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 anti-resorptive agent, 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.
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.

Atypical femoral fractures
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.

General
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.

In post-marketing experience, there have been rare reports of severe skin reactions including Stevens Johnson syndrome and toxic epidermal necrolysis associated with alendronate.
Causes of osteoporosis other than oestrogen deficiency and ageing should be considered.

Co-administration with tetracyclines or quinolones is usually not recommended, or must be done with precaution (see section 4.5).

Lactose and Sucrose:
Alendronate tablets contain 122.21 mg lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.
Calcium/cholecalciferol tablets contain 1.75 mg sucrose. Patients with rare hereditary problems of

fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Sodium:
This medicine 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 70 mg
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 drug 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.

Calcium/cholecalciferol
Thiazide diuretics reduce the urinary excretion of calcium. Due to increased risk of hypercalcaemia, serum calcium should be regularly monitored during concomitant use of thiazide diuretics.

Concomitant use of phenytoin or barbiturates may reduce the effect of vitamin D_3 since the metabolism increases.

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

Hypercalcaemia may increase the toxicity of cardiac glycosides during treatment with calcium and vitamin D. Patients should be monitored with regard to electrocardiogram (ECG) and serum calcium levels.

The efficacy of levothyroxine can be reduced by the concurrent use of calcium, due to decreased levothyroxine absorption. Administration of calcium and levothyroxine should be separated by at least four hours.

The gastrointestinal absorption of alendronate may be reduced by calcium. Patients should be instructed never to take calcium/cholecalciferol tablets on the same day as Alendronate tablets (see section 4.2 and 4.4).

Calcium salts may decrease the absorption of iron, zinc and strontium ranelate. Consequently, iron, zinc or strontium ranelate preparations should be taken at least two hours before or after the calcium/cholecalciferol tablet.

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

Treatment with orlistat may potentially impair the absorption of fat-soluble vitamins (e.g. vitamin D_3).

Calcium may interfere with the absorption of concomitantly 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.

The absorption of quinolone antibiotics may be impaired if administered concomitantly with calcium. Quinolone antibiotics should be taken two hours before or six hours after intake of calcium.

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 high in oxalic acid and phytic acid.

4.6 Fertility, pregnancy and lactation

Tridepos is intended for use in postmenopausal women and should not be used during pregnancy or while breastfeeding.

Pregnancy
Tridepos should not be used during pregnancy. There are no adequate data from the use of Tridepos or alendronate or calcium and vitamin D 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).

During pregnancy the daily intake should not exceed 1500 mg calcium and 600 IU vitamin D. Studies in animals have shown reproductive toxicity of high doses of vitamin D (see section 5.3). In pregnant women, overdoses of calcium and vitamin D should be avoided as permanent hypercalcaemia has been related to adverse effects on the developing foetus.

Breast-feeding
Calcium and vitamin D_3 pass into breast milk. It is not known whether alendronate/metabolites are excreted into human milk. A risk to the newborns/infants cannot be excluded. Tridepos should not be used during breast-feeding.

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/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 Tridepos may vary (see section 4.8).

4.8 Undesirable effects

Alendronate 70 mg tablet

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

[Very common (≥1/10), Common (≥1/100, <1/10), Uncommon (≥1/1,000, <1/100), Rare (≥1/10,000, <1/1,000), 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.[§]
Nervous system disorders:	*Common:* headache, dizziness[†] *Uncommon:* dysgeusia[†]
Eye disorders:	*Uncommon:* eye inflammation (uveitis, scleritis, episcleritis)
Ear and labyrinth disorders:	*Common:* vertigo[†] *Very rare:* Osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction)
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 conditions:	*Common:* asthenia[†], peripheral oedema[†] *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*
[⊥]*Identified in postmarketing experience.*

Calcium/cholecalciferol tablets

Adverse drug reactions are listed below.

Adverse reactions frequencies are defined as: uncommon (≥1/1,000, <1/100), rare (>1/10,000, <1/1,000) or not known (cannot be estimated from the available data).

Immune system disorders	*Not known (cannot be estimated from the available data):* Hypersensitivity reactions such as angioedema or laryngeal oedema.
Metabolism and nutrition disorders	*Uncommon:* Hypercalcaemia and hypercalciuria.
Gastrointestinal disorders	*Rare:* Constipation, flatulence, nausea, abdominal pain, and diarrhoea.
Skin and subcutaneous disorders	*Rare:* Pruritus, rash and urticaria.

Special populations
Patients with renal impairment are at potential risk of hyperphosphaetemia, nephrolithiasis and nephrocalcinosis.

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the risk/benefit balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V*.

4.9 Overdose

Alendronate 70 mg
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.

Calcium/cholecalciferol
Overdose can lead to hypervitaminosis 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: The treatment with calcium and vitamin D must be discontinued. Treatment with thiazide diuretics, lithium, vitamin A, vitamin D and cardiac glycosides must also be discontinued. 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 CVP should be followed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Alendronic acid, calcium and cholecalciferol, sequentially
ATC code: M05BB05

Alendronate 70 mg

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

Treatment of post-menopausal osteoporosis
The effects of alendronate 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 alendronate 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 alendronate 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 using alendronate daily (5 mg daily for two years and 10 mg daily for either one or two additional years):
• FIT 1: A three-year study of 2,027 patients who 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% vs. placebo 15.0%). In addition, a statistically significant reduction was found in the incidence of hip fractures (1.1% vs. 2.2%, a reduction of 51%).
• FIT 2: A four-year study of 4,432 patients with low bone mass but without a baseline vertebral fracture. In this study, a significant difference was observed in the analysis of the subgroup of osteoporotic women (37% of the global population who correspond with the above definition of osteoporosis) in the incidence of hip fractures (alendronate 1.0% vs. placebo 2.2%, a reduction of 56%) and in the incidence of ≥1 vertebral fracture (2.9% vs. 5.8%, a reduction of 50%).

Bisphosphonates have been shown to reduce the risk of fractures when given in combination with calcium and vitamin D supplements.

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 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.

<u>Calcium/cholecalciferol</u>
Vitamin D increases the intestinal absorption of calcium.
Administration of calcium and vitamin D_3 counteracts the increase of parathyroid hormone (PTH), which is caused by calcium deficiency and which causes increased bone resorption.

A clinical study of institutionalised patients suffering from vitamin D deficiency indicated that a daily intake of 1000 mg calcium and 800 IU cholecalciferol for six months normalised the value of the 25-hydroxylated metabolite of vitamin D3 and reduced secondary hyperparathyroidism and alkaline phosphatases.

An 18 month double-blind, placebo controlled study including 3270 institutionalised women aged 84+/- 6 years who received supplementation of vitamin D (800 IU/day) and calcium phosphate (corresponding to 1200 mg/day of elemental calcium), showed a significant decrease of PTH

secretion. After 18 months, an "intent-to treat" analysis showed 80 hip fractures in the calcium-vitamin D group and 110 hip fractures in the placebo group (p=0.004).

5.2 Pharmacokinetic properties

Alendronate

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 to an estimated 0.46% and 0.39% when alendronate was administered one hour or half an hour before a standardised breakfast. In osteoporosis studies, Alendronate was effective when administered at least 30 minutes before the first food or beverage of the day.

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

In healthy subjects, oral prednisone (20 mg three times daily for five days) did not produce a clinically meaningful change in 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 [^{14}C] alendronate, approximately 50% of the radioactivity was excreted in the urine within 72 hours and little or no radioactivity was recovered in the faeces. Following a single 10 mg IV dose, the renal clearance of alendronate was 71 ml/min, and systemic clearance did not exceed 200 ml/min. Plasma concentrations fell by more than 95% within six 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 that is not deposited in bone is rapidly excreted in the urine. No evidence of saturation of bone uptake was found after chronic dosing with cumulative IV doses up to 35 mg/kg in animals. Although no clinical information is available, it is likely that, as in animals, elimination of alendronate via the kidney will be reduced in patients with impaired renal function. Therefore, somewhat greater accumulation of alendronate in bone might be expected in patients with impaired renal function (see section 4.2).

Calcium

Absorption: The amount of calcium absorbed through the gastrointestinal tract is approximately 30% of the swallowed dose.

Distribution and metabolism: 99% of the 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 in the physiologically active ionised form with approximately 10% being complexed to citrate, phosphate or other anions, the remaining 40% being bound to proteins, principally albumin. The bioavailability of calcium can be slightly increased by concomitant intake of food.

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

Cholecalciferol
Absorption: Vitamin D is easily absorbed in the small intestine.
Distribution and metabolism: 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- dihydroxycholecalciferol. 1,25-dihydroxycholecalciferol is the metabolite responsible for increasing calcium absorption. Vitamin D which 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
Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. Studies in rats have shown that treatment with alendronic acid 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.

Calcium/cholecalciferol
At vitamin D doses far higher than the human therapeutic range teratogenicity has been observed in animal studies. There is further no 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

Alendronate tablet
Lactose monohydrate
Microcrystalline cellulose
Croscarmellose sodium
Magnesium stearate
Silica colloidal anhydrous

Calcium/cholecalciferol tablet
Core:
Maltodextrin
Croscarmellose sodium
Silica, colloidal anhydrous
Magnesium stearate
all-*rac*-alpha-tocopherol
Sucrose
Medium chain triglycerides
Starch sodium octenyl succinate (E 1450)

Silicon dioxide
Sodium ascorbate
Coating:
Hypromellose
Macrogol
Paraffin

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

30 months

6.4 Special precautions for storage

Store below 30°C. Store in the original package in order to protect from light and moisture.

6.5 Nature and content of container

The tablets are packed in opaque PVC/PE/PVDC blisters sealed with Aluminium foil. Each blister contains one alendronate tablet and six calcium/cholecalciferol tablets. Each cavity has a day marking (Day 1, Day 2, …Day 7) for sequential administration.

Pack sizes are packs with 4 blisters in a carton and packs with 12 blisters in a carton. Each blister contains 1 alendronate tablet and 6 calcium/cholecalciferol tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8 MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: [To be completed nationally]
Date of latest renewal: 8 April 2021

10 DATE OF REVISION OF THE TEXT

2021-11-15