ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
1. NAME OF THE MEDICINAL PRODUCT

ALENDRONATE SODIUM AND COLECALCIFEROL, MSD 70 mg/2800 IU tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 70 mg alendronic acid as alendronate sodium trihydrate, and 70 micrograms (2800 IU) colecalciferol (vitamin D₃).

Excipients:
Each tablet contains 62 mg lactose anhydrous and 8 mg sucrose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

Capsule-shaped, white to off-white tablets, marked with an outline of a bone image on one side, and '710' on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of postmenopausal osteoporosis in patients at risk of vitamin D insufficiency. ALENDRONATE SODIUM AND COLECALCIFEROL, MSD reduces the risk of vertebral and hip fractures.

4.2 Posology and method of administration

The recommended dosage is one ALENDRONATE SODIUM AND COLECALCIFEROL, MSD tablet once weekly.

Due to the nature of the disease process in osteoporosis, ALENDRONATE SODIUM AND COLECALCIFEROL, MSD is intended for long-term use.

To permit adequate absorption of alendronate:

ALENDRONATE SODIUM AND COLECALCIFEROL, MSD must be taken with water only (not mineral water) at least 30 minutes before the first food, beverage, or medicinal product (including antacids, calcium supplements and vitamins) of the day. Other beverages (including mineral water), food and some medicinal products are likely to reduce the absorption of alendronate (see section 4.5).

The following instructions should be followed exactly in order to minimize the risk of oesophageal irritation and related adverse reactions (see section 4.4):

- ALENDRONATE SODIUM AND COLECALCIFEROL, MSD should only be swallowed after getting up for the day with a full glass of water (not less than 200 ml or 7 fl.oz.).
- Patients should only swallow ALENDRONATE SODIUM AND COLECALCIFEROL, MSD 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 SODIUM AND COLECALCIFEROL, MSD.

• ALENDRONATE SODIUM AND COLECALCIFEROL, MSD should not be taken at bedtime or before arising for the day.

Patients should receive supplemental calcium if intake from diet is inadequate (see section 4.4). Additional supplementation with vitamin D should be considered on an individual basis taking into account any vitamin D intake from vitamins and dietary supplements. The equivalence of intake of 2800 IU of vitamin D3 weekly in ALENDRONATE SODIUM AND COLECALCIFEROL, MSD to daily dosing of vitamin D 400 IU has not been studied.

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 impairment:
No dosage adjustment is necessary for patients with a glomerular filtration rate (GFR) greater than 35 ml/min. ALENDRONATE SODIUM AND COLECALCIFEROL, MSD is not recommended for patients with renal impairment where GFR is less than 35 ml/min, due to lack of experience.

Use in children and adolescents:
ALENDRONATE SODIUM AND COLECALCIFEROL, MSD has not been studied in children and adolescents and therefore should not be given to them.

4.3 Contraindications

• Hypersensitivity to the active substances or to any of the excipients.

• 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.

• Hypocalcaemia.

4.4 Special warnings and precautions for use

Alendronate
Alendronate can cause local irritation of the upper gastrointestinal 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 gastrointestinal problems, such as dysphagia, oesophageal disease, gastritis, duodenitis, ulcers, or with a recent history (within the previous year) of major gastrointestinal disease such as peptic ulcer, or active gastrointestinal bleeding, or surgery of the upper gastrointestinal tract other than pyloroplasty (see section 4.3).

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 or new or worsening heartburn (see section 4.8).
The risk of severe oesophageal adverse reactions 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 are 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 with alendronate, there have been rare (post-marketing) reports of gastric and duodenal ulcers, some of which were severe and with complications (see section 4.8).

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.

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

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

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

Bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates. In post-marketing experience, these symptoms have rarely been severe and/or incapacitating (see 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 treatment. A subset had recurrence of symptoms when rechallenged with the same medicinal product or another bisphosphonate.

Stress fractures (also known as insufficiency fractures) of the proximal femoral shaft have been reported in patients treated long-term with alendronic acid (time to onset in the majority of cases ranged from 18 months to 10 years). The fractures occurred after minimal or no trauma and some patients experienced thigh pain, often associated with imaging features of stress fractures, weeks to months before presenting with a completed femoral fracture. Fractures were 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 was also reported. Discontinuation of bisphosphonate therapy in patients with stress fracture is advisable pending evaluation of the patient, based on an individual benefit risk assessment.

Patients should be instructed that if they miss a dose of ALENDRONATE SODIUM AND COLECALCIFEROL, MSD they should take one tablet on the morning after they remember. They should not take two tablets on the same day but should return to taking one tablet once a week, as originally scheduled on their chosen day.

ALENDRONATE SODIUM AND COLECALCIFEROL, MSD 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 SODIUM AND COLECALCIFEROL, MSD (see section 4.3). Other disorders affecting mineral metabolism (such as vitamin D deficiency and hypoparathyroidism) should also be effectively treated before starting
ALENDRONATE SODIUM AND COLECALCIFEROL, MSD. The content of vitamin D in ALENDRONATE SODIUM AND COLECALCIFEROL, MSD is not suitable for correction of vitamin D deficiency. In patients with these conditions, serum calcium and symptoms of hypocalcaemia should be monitored during therapy with ALENDRONATE SODIUM AND COLECALCIFEROL, MSD.

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) (see section 4.8).

Colecalciferol
Vitamin D₃ may increase the magnitude of hypercalcaemia and/or hypercalciuria when administered to patients with disease associated with unregulated overproduction of calcitriol (e.g. leukaemia, lymphoma, sarcoidosis). Urine and serum calcium should be monitored in these patients.

Patients with malabsorption may not adequately absorb vitamin D₃.

Excipients
This medicinal product contains lactose and sucrose. Patients with rare hereditary problems of fructose intolerance, galactose intolerance, the Lapp lactase deficiency, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicinal product.

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 clinically significant interactions with medicinal products are anticipated. A number of patients in the clinical trials received oestrogen (intravaginal, transdermal, or oral) while taking alendronate. No adverse reactions 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 interactions of clinical relevance.

Colecalciferol
Olestra, mineral oils, orlistat, and bile acid sequestrants (e.g. cholestyramine, colestipol) may impair the absorption of vitamin D. Anticonvulsants, cimetidine and thiazides may increase the catabolism of vitamin D. Additional vitamin D supplements may be considered on an individual basis.

4.6 Pregnancy and lactation

ALENDRONATE SODIUM AND COLECALCIFEROL, MSD is only intended for use in postmenopausal women and therefore it should not be used during pregnancy or in breast-feeding women.

There are no adequate data from the use of ALENDRONATE SODIUM AND COLECALCIFEROL, MSD in pregnant women. Animal studies with alendronate do not indicate direct harmful effects with
respect to pregnancy, embryonal/foetal development, or postnatal development. Alendronate given
during pregnancy in rats caused dystocia related to hypocalcaemia (see section 5.3). Studies in animals
have shown hypercalcaemia and reproductive toxicity with high doses of vitamin D (see section 5.3).

It is not known whether alendronate is excreted into human breast milk. Colecalciferol and some of its
active metabolites pass into breast milk.

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 SODIUM AND
COLECALCIFEROL, MSD may affect some patients' ability to drive or operate machinery.
Individual responses to ALENDRONATE SODIUM AND COLECALCIFEROL, MSD may vary (see
section 4.8).

4.8 Undesirable effects

The following adverse reactions have been reported during clinical studies and/or post-marketing use
with alendronate.

No additional adverse reactions have been identified for ALENDRONATE SODIUM AND
COLECALCIFEROL, MSD.

[Common (≥ 1/100, < 1/10), uncommon (≥ 1/1,000, < 1/100), rare (≥ 1/10,000, < 1/1,000), very rare
(< 1/10,000)]

| Nervous system disorders: | Common: headache |
| Eye disorders: | Rare: uveitis, scleritis, episcleritis |
| Gastrointestinal disorders: | Common: abdominal pain, dyspepsia, constipation, diarrhoea, flatulence, oesophageal ulcer*, dysphagia*, abdominal distension, acid regurgitation Uncommon: nausea, vomiting, gastritis, oesophagitis*, oesophageal erosions*, melena Rare: oesophageal stricture*, oropharyngeal ulceration*, upper gastrointestinal PUBs (perforation, ulcers, bleeding)(see section 4.4). |
*See sections 4.2 and 4.4 |
| Skin and subcutaneous tissue disorders: | Uncommon: rash, pruritus, erythema Rare: rash with photosensitivity Very rare: severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis |
| Musculoskeletal and connective tissue disorders: | Common: musculoskeletal (bone, muscle or joint) pain Rare: severe musculoskeletal (bone, muscle or joint) pain (see section 4.4) |
| Metabolism and nutrition disorders: | Rare: symptomatic hypocalcaemia, often in association with predisposing conditions. (see section 4.4) |
| General disorders and administration site conditions: | Rare: transient symptoms as in an acute-phase response (myalgia, malaise and rarely, fever), typically in association with initiation of treatment. |
| Immune system disorders: | Rare: hypersensitivity reactions including urticaria and angioedema |

During post-marketing experience the following reactions have been reported (frequency not known):

| Nervous system disorders: | Dizziness, dysgeusia |
| Ear and labyrinth disorders: | Vertigo |
| Skin and subcutaneous tissue disorders: | Alopecia |
Musculoskeletal, connective tissue and bone disorders:

Osteonecrosis of the jaw has been reported in patients treated by bisphosphonates. The majority of the reports refer to cancer patients, but such cases have also been reported in patients treated for osteoporosis. Osteonecrosis of the jaw is generally associated with tooth extraction and / or local infection (including osteomyelitis). Diagnosis of cancer, chemotherapy, radiotherapy, corticosteroids and poor oral hygiene are also deemed as risk factors (see section 4.4); joint swelling; stress fractures of the proximal femoral shaft (see section 4.4)

General disorders and administration site conditions:

asthenia, peripheral oedema

Laboratory test findings

In clinical studies, asymptomatic, mild and transient decreases in serum calcium and phosphate were observed in approximately 18 % and 10 %, respectively, of patients taking 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.

4.9 Overdose

Alendronate

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

No specific information is available on the treatment of overdose with alendronate. In case of overdose with ALENDRONATE SODIUM AND COLECALCIFEROL, MSD, 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.

Colecalciferol

Vitamin D toxicity has not been documented during chronic therapy in generally healthy adults at a dose less than 10,000 IU/day. In a clinical study of healthy adults a 4,000 IU daily dose of vitamin D₃ for up to five months was not associated with hypercalciuria or hypercalcaemia.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Bisphosphonates, combinations, ATC code: M05BB03.

ALENDRONATE SODIUM AND COLECALCIFEROL, MSD is a combination tablet containing the two active substances alendronate sodium trihydrate and colecalciferol (vitamin D₃).

Alendronate

Alendronate sodium is a bisphosphonate that inhibits osteoclastic bone resorption with no direct effect on bone formation. Preclinical studies have shown preferential localisation of alendronate to sites of active resorption. Activity of osteoclasts is inhibited, but recruitment or attachment of osteoclasts is not affected. The bone formed during treatment with alendronate is of normal quality.

Colecalciferol (vitamin D₃)

Vitamin D₃ is produced in the skin by conversion of 7-dehydrocholesterol to vitamin D₃ by ultraviolet light. In the absence of adequate sunlight exposure, vitamin D₃ is an essential dietary nutrient. Vitamin D₃ is converted to 25-hydroxyvitamin D₃ in the liver, and stored until needed. Conversion to the active calcium-mobilizing hormone 1,25-dihydroxyvitamin D₃ (calcitriol) in the kidney is tightly regulated. The principal action of 1,25-dihydroxyvitamin D₃ is to increase intestinal absorption of both calcium
and phosphate as well as regulate serum calcium, renal calcium and phosphate excretion, bone formation and bone resorption.

Vitamin D₃ is required for normal bone formation. Vitamin D insufficiency develops when both sunlight exposure and dietary intake are inadequate. Insufficiency is associated with negative calcium balance, bone loss, and increased risk of skeletal fracture. In severe cases, deficiency results in secondary hyperparathyroidism, hypophosphataemia, proximal muscle weakness and osteomalacia, further increasing the risk of falls and fractures in osteoporotic individuals. Supplemental vitamin D reduces these risks and their consequences.

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

**ALENDRONATE SODIUM AND COLECALCIFEROL, MSD studies**

The effect of ALENDRONATE SODIUM AND COLECALCIFEROL, MSD (alendronate 70 mg/vitamin D₃ 2800 IU) on vitamin D status was demonstrated in a 15-week, multinational study that enrolled 682 osteoporotic post-menopausal women (serum 25-hydroxyvitamin D at baseline: mean, 56 nmol/l [22.3 ng/ml]; range, 22.5-225 nmol/l [9-90 ng/ml]). Patients received the lower strength (70 mg/2800 IU) of ALENDRONATE SODIUM AND COLECALCIFEROL, MSD (n=350) or FOSAMAX (alendronate) 70 mg (n=332) once a week; additional vitamin D supplements were prohibited. After 15 weeks of treatment, the mean serum 25-hydroxyvitamin D levels were significantly higher (26 %) in the ALENDRONATE SODIUM AND COLECALCIFEROL, MSD (70 mg/2800 IU) group (56 nmol/l [23 ng/ml]) than in the alendronate-only group (46 nmol/l [18.2 ng/ml]). The percentage of patients with vitamin D insufficiency (serum 25-hydroxyvitamin D < 37.5 nmol/l [< 15 ng/ml]) was significantly reduced by 62.5 % with ALENDRONATE SODIUM AND COLECALCIFEROL, MSD (70 mg/2800 IU) vs. alendronate-only (12 % vs. 32 %, respectively), through week 15. The percentage of patients with vitamin D deficiency (serum 25-hydroxyvitamin D < 22.5 nmol/l [< 9 ng/ml]) was significantly reduced by 92 % with ALENDRONATE SODIUM AND COLECALCIFEROL, MSD (70 mg/2800 IU) vs. alendronate-only (1 % vs 13 %, respectively). In this study, mean 25-hydroxyvitamin D levels in patients with vitamin D insufficiency at baseline (25-hydroxyvitamin D, 22.5 to 37.5 nmol/l [9 to < 15 ng/ml]) increased from 30 nmol/l (12.1 ng/ml) to 40 nmol/l (15.9 ng/ml) at week 15 in the ALENDRONATE SODIUM AND COLECALCIFEROL, MSD (70 mg/2800 IU) group (n=75) and decreased from 30 nmol/l (12.0 ng/ml) at baseline to 26 nmol/l (10.4 ng/ml) at week 15 in the alendronate-only group (n=70). There were no differences in mean serum calcium, phosphate, or 24-hour urine calcium between treatment groups.

**Alendronate studies**

The therapeutic equivalence of alendronate once weekly 70 mg (n=519) and alendronate 10 mg daily (n=370) was demonstrated in a one-year multicentre study of post-menopausal women with osteoporosis. The mean increases from baseline in lumbar spine BMD at one year were 5.1 % (95 % CI: 4.8, 5.4 %) in the 70 mg once-weekly group and 5.4 % (95 % CI: 5.0, 5.8 %) in the 10 mg daily group. The mean BMD increases were 2.3 % and 2.9 % at the femoral neck and 2.9 % and 3.1 % at the total hip in the 70 mg once weekly and 10 mg daily groups, respectively. The two treatment groups were also similar with regard to BMD increases at other skeletal sites.

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 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 (alendronate 3.2 % vs placebo 6.2 %) 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 $\geq 1$ 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 $\geq 1$ vertebral fracture (2.9 % vs. 5.8 %, a reduction of 50 %).

### 5.2. Pharmacokinetic properties

**Alendronate**

**Absorption**

Relative to an intravenous reference dose, the oral mean bioavailability of alendronate in women was 0.64 % for doses ranging from 5 to 70 mg when administered after an overnight fast and two hours before a standardised breakfast. 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.

The alendronate component in the ALENDRONATE SODIUM AND COLECALCIFEROL, MSD (70 mg/2800 IU) combination tablet is bioequivalent to the alendronate 70 mg tablet.

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 intravenous 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 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 [14C]alendronate, approximately 50 % of the radioactivity was excreted in the urine within 72 hours and little or no radioactivity was recovered in the faeces. Following a single 10 mg intravenous 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 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 anticipated to interfere with the excretion of other medicinal products by those systems in humans.

**Colecalciferol**

**Absorption**

In healthy adult subjects (males and females), following administration of ALENDRONATE SODIUM AND COLECALCIFEROL, MSD after an overnight fast and two hours before a meal, the mean area under the serum-concentration-time curve (AUC$_{0-120\text{hrs}}$) for vitamin D$_3$ (unadjusted for endogenous vitamin D$_3$ levels) was 296.4 ng•hr/ml. The mean maximal serum concentration ($C_{\text{max}}$) of vitamin D$_3$ was 5.9 ng/ml, and the median time to maximal serum concentration ($T_{\text{max}}$) was 12 hours. The bioavailability of the 2800 IU vitamin D$_3$ in ALENDRONATE SODIUM AND COLECALCIFEROL, MSD is similar to 2800 IU vitamin D$_3$ administered alone.

**Distribution**

Following absorption, vitamin D$_3$ enters the blood as part of chylomicrons. Vitamin D$_3$ is rapidly distributed mostly to the liver where it undergoes metabolism to 25-hydroxyvitamin D$_3$, the major storage form. Lesser amounts are distributed to adipose and muscle tissue and stored as vitamin D$_3$ at these sites for later release into the circulation. Circulating vitamin D$_3$ is bound to vitamin D-binding protein.

**Biotransformation**

Vitamin D$_3$ is rapidly metabolized by hydroxylation in the liver to 25-hydroxyvitamin D$_3$, and subsequently metabolized in the kidney to 1,25-dihydroxyvitamin D$_3$, which represents the biologically active form. Further hydroxylation occurs prior to elimination. A small percentage of vitamin D$_3$ undergoes glucuronidation prior to elimination.

**Elimination**

When radioactive vitamin D$_3$ was administered to healthy subjects, the mean urinary excretion of radioactivity after 48 hours was 2.4 %, and the mean faecal excretion of radioactivity after 4 days was 4.9 %. In both cases, the excreted radioactivity was almost exclusively as metabolites of the parent. The mean half-life of vitamin D$_3$ in the serum following an oral dose of ALENDRONATE SODIUM AND COLECALCIFEROL, MSD (70 mg/2800 IU) is approximately 24 hours.

**Characteristics in patients**

Preclinical studies show that alendronate 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 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).

5.3 **Preclinical safety data**

Non-clinical studies with the combination of alendronate and colecalciferol have not been conducted.

**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 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.

**Colecalciferol**

At doses far higher than the human therapeutic range, reproductive toxicity has been observed in animal studies.
6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose (E460)
Lactose anhydrous
Medium chain triglycerides
Gelatin
Croscarmellose sodium
Sucrose
Colloidal silicon dioxide
Magnesium stearate (E572)
Butyl hydroxytoluene (E321)
Modified starch (maize)
Sodium aluminium silicate (E554)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months.

6.4 Special precautions for storage

Store in the original blister in order to protect from moisture and light.

6.5 Nature and contents of container

Wallet with sealed aluminium/aluminium blisters, in cartons containing 2 (1 wallet x 2 tablets), 4 (1 wallet x 4 tablets), 6 (3 wallets x 2 tablets), 12 (3 wallets x 4 tablets) or 40 (10 wallets x 4 tablets) tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER(S)

Merck Sharp & Dohme Ltd.
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/00/000/000 – 2 tablets
EU/00/000/000 – 4 tablets
EU/00/000/000 – 6 tablets
EU/00/000/000 – 12 tablets
EU/00/000/000 – 40 tablets
9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

10. DATE OF REVISION OF THE TEXT
1. **NAME OF THE MEDICINAL PRODUCT**

ALENDRONATE SODIUM AND COLECALCIFEROL, MSD 70 mg/5600 IU tablets

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each tablet contains 70 mg alendronic acid as alendronate sodium trihydrate and 140 micrograms (5600 IU) colecalciferol (vitamin D₃).

Excipients:
Each tablet contains 63 mg lactose anhydrous and 16 mg sucrose.

For a full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Tablet.

Modified rectangle-shaped, white to off-white tablets, marked with an outline of a bone image on one side, and ‘270’ on the other.

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

Treatment of postmenopausal osteoporosis in patients who are not receiving vitamin D supplementation and are at risk of vitamin D insufficiency.

ALENDRONATE SODIUM AND COLECALCIFEROL, MSD reduces the risk of vertebral and hip fractures.

4.2 **Posology and method of administration**

The recommended dosage is one ALENDRONATE SODIUM AND COLECALCIFEROL, MSD tablet once weekly.

Due to the nature of the disease process in osteoporosis, ALENDRONATE SODIUM AND COLECALCIFEROL, MSD is intended for long-term use.

*To permit adequate absorption of alendronate:*

ALENDRONATE SODIUM AND COLECALCIFEROL, MSD must be taken with water only (not mineral water) at least 30 minutes before the first food, beverage, or medicinal product (including antacids, calcium supplements and vitamins) of the day. Other beverages (including mineral water), food and some medicinal products are likely to reduce the absorption of alendronate (see section 4.5).

*The following instructions should be followed exactly in order to minimize the risk of oesophageal irritation and related adverse reactions (see section 4.4):*

- ALENDRONATE SODIUM AND COLECALCIFEROL, MSD should only be swallowed after getting up for the day with a full glass of water (not less than 200 ml or 7 fl.oz.).
- Patients should only swallow ALENDRONATE SODIUM AND COLECALCIFEROL, MSD 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 SODIUM AND COLECALCIFEROL, MSD.

• ALENDRONATE SODIUM AND COLECALCIFEROL, MSD should not be taken at bedtime or before arising for the day.

Patients should receive supplemental calcium if intake from diet is inadequate (see section 4.4). The equivalence of intake of 5600 IU of vitamin D3 weekly in ALENDRONATE SODIUM AND COLECALCIFEROL, MSD to daily dosing of vitamin D 800 IU has not been studied.

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 impairment:
No dosage adjustment is necessary for patients with a glomerular filtration rate (GFR) greater than 35 ml/min. ALENDRONATE SODIUM AND COLECALCIFEROL, MSD is not recommended for patients with renal impairment where GFR is less than 35 ml/min, due to lack of experience.

Use in children and adolescents:
ALENDRONATE SODIUM AND COLECALCIFEROL, MSD has not been studied in children and adolescents and therefore should not be given to them.

4.3 Contraindications

• Hypersensitivity to the active substances or to any of the excipients.

• 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.

• Hypocalcaemia.

4.4 Special warnings and precautions for use

Alendronate
Alendronate can cause local irritation of the upper gastrointestinal 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 gastrointestinal problems, such as dysphagia, oesophageal disease, gastritis, duodenitis, ulcers, or with a recent history (within the previous year) of major gastrointestinal disease such as peptic ulcer, or active gastrointestinal bleeding, or surgery of the upper gastrointestinal tract other than pyloroplasty (see section 4.3).

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 or new or worsening heartburn (see section 4.8).

The risk of severe oesophageal adverse reactions 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 are 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 with alendronate, there have been rare (post-marketing) reports of gastric and duodenal ulcers, some of which were severe and with complications (see section 4.8).

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.

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

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

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

Bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates. In post-marketing experience, these symptoms have rarely been severe and/or incapacitating (see 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 treatment. A subset had recurrence of symptoms when rechallenged with the same medicinal product or another bisphosphonate.

Stress fractures (also known as insufficiency fractures) of the proximal femoral shaft have been reported in patients treated long-term with alendronic acid (time to onset in the majority of cases ranged from 18 months to 10 years). The fractures occurred after minimal or no trauma and some patients experienced thigh pain, often associated with imaging features of stress fractures, weeks to months before presenting with a completed femoral fracture. Fractures were 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 was also reported. Discontinuation of bisphosphonate therapy in patients with stress fracture is advisable pending evaluation of the patient, based on an individual benefit risk assessment.

Patients should be instructed that if they miss a dose of ALENDRONATE SODIUM AND COLECALCIFEROL, MSD they should take one tablet on the morning after they remember. They should not take two tablets on the same day but should return to taking one tablet once a week, as originally scheduled on their chosen day.

ALENDRONATE SODIUM AND COLECALCIFEROL, MSD 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 SODIUM AND COLECALCIFEROL, MSD (see section 4.3). Other disorders affecting mineral metabolism (such as vitamin D deficiency and hypoparathyroidism) should also be effectively treated before starting ALENDRONATE SODIUM AND COLECALCIFEROL, MSD. The content of vitamin D in ALENDRONATE SODIUM AND COLECALCIFEROL, MSD is not suitable for correction of
vitamin D deficiency. In patients with these conditions, serum calcium and symptoms of hypocalcaemia should be monitored during therapy with ALENDRONATE SODIUM AND COLECALCIFEROL, MSD.

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) (see section 4.8).

Colecalciferol
Vitamin D₃ may increase the magnitude of hypercalcaemia and/or hypercalciuria when administered to patients with disease associated with unregulated overproduction of calcitriol (e.g. leukaemia, lymphoma, sarcoidosis). Urine and serum calcium should be monitored in these patients.

Patients with malabsorption may not adequately absorb vitamin D₃.

Excipients
This medicinal product contains lactose and sucrose. Patients with rare hereditary problems of fructose intolerance, galactose intolerance, the Lapp lactase deficiency, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicinal product.

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 clinically significant interactions with medicinal products are anticipated. A number of patients in the clinical trials received oestrogen (intravaginal, transdermal, or oral) while taking alendronate. No adverse reactions 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 interactions of clinical relevance.

Colecalciferol
Olestra, mineral oils, orlistat, and bile acid sequestrants (e.g. cholestyramine, colestipol) may impair the absorption of vitamin D. Anticonvulsants, cimetidine and thiazides may increase the catabolism of vitamin D. Additional vitamin D supplements may be considered on an individual basis.

4.6 Pregnancy and lactation

ALENDRONATE SODIUM AND COLECALCIFEROL, MSD is only intended for use in postmenopausal women and therefore it should not be used during pregnancy or in breast-feeding women.

There are no adequate data from the use of ALENDRONATE SODIUM AND COLECALCIFEROL, MSD in pregnant women. Animal studies with alendronate do not indicate direct harmful effects with respect to pregnancy, embryonal/foetal development, or postnatal development. Alendronate given
during pregnancy in rats caused dystocia related to hypocalcaemia (see section 5.3). Studies in animals have shown hypercalcaemia and reproductive toxicity with high doses of vitamin D (see section 5.3).

It is not known whether alendronate is excreted into human breast milk. Colecalciferol and some of its active metabolites pass into breast milk.

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 SODIUM AND COLECALCIFEROL, MSD may affect some patients’ ability to drive or operate machinery. Individual responses to ALENDRONATE SODIUM AND COLECALCIFEROL, MSD may vary (see section 4.8).

4.8 Undesirable effects

The following adverse reactions have been reported during clinical studies and/or post-marketing use with alendronate.

No additional adverse reactions have been identified for ALENDRONATE SODIUM AND COLECALCIFEROL, MSD.

[Common (≥1/100, < 1/10), uncommon (≥1/1,000, < 1/100), rare (≥1/10,000, < 1/1,000), very rare (<1/10,000)]

<table>
<thead>
<tr>
<th>Nervous system disorders:</th>
<th>Common: headache</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye disorders:</td>
<td>Rare: uveitis, scleritis, episcleritis</td>
</tr>
<tr>
<td>Gastrointestinal disorders:</td>
<td>Common: abdominal pain, dyspepsia, constipation, diarrhoea, flatulence, oesophageal ulcer*, dysphagia*, abdominal distension, acid regurgitation Uncommon: nausea, vomiting, gastritis, oesophagitis*, oesophageal erosions*, melena Rare: oesophageal stricture*, oropharyngeal ulceration*, upper gastrointestinal PUBs (perforation, ulcers, bleeding)(see section 4.4). *See sections 4.2 and 4.4</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders:</td>
<td>Uncommon: rash, pruritus, erythema rare: rash with photosensitivity Very rare: severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders:</td>
<td>Common: musculoskeletal (bone, muscle or joint) pain Rare: severe musculoskeletal (bone, muscle or joint) pain (see section 4.4)</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders:</td>
<td>Rare: symptomatic hypocalcaemia, often in association with predisposing conditions. (see section 4.4)</td>
</tr>
<tr>
<td>General disorders and administration site conditions:</td>
<td>Rare: transient symptoms as in an acute-phase response (myalgia, malaise and rarely, fever), typically in association with initiation of treatment.</td>
</tr>
<tr>
<td>Immune system disorders:</td>
<td>Rare: hypersensitivity reactions including urticaria and angioedema</td>
</tr>
</tbody>
</table>

During post-marketing experience the following reactions have been reported (frequency not known):

<table>
<thead>
<tr>
<th>Nervous system disorders:</th>
<th>Dizziness, dysgeusia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ear and labyrinth disorders:</td>
<td>Vertigo</td>
</tr>
</tbody>
</table>
Skin and subcutaneous tissue disorders: Alopecia

Musculoskeletal, connective tissue and bone disorders: Osteonecrosis of the jaw has been reported in patients treated by bisphosphonates. The majority of the reports refer to cancer patients, but such cases have also been reported in patients treated for osteoporosis. Osteonecrosis of the jaw is generally associated with tooth extraction and/or local infection (including osteomyelitis). Diagnosis of cancer, chemotherapy, radiotherapy, corticosteroids and poor oral hygiene are also deemed as risk factors (see section 4.4); joint swelling; stress fractures of the proximal femoral shaft (see section 4.4).

General disorders and administration site conditions: asthenia, peripheral oedema

Laboratory test findings
In clinical studies, asymptomatic, mild and transient decreases in serum calcium and phosphate were observed in approximately 18% and 10%, respectively, of patients taking 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.

4.9 Overdose

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

No specific information is available on the treatment of overdose with alendronate. In case of overdose with ALENDRONATE SODIUM AND COLECALCIFEROL, MSD, 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.

Colecalciferol
Vitamin D toxicity has not been documented during chronic therapy in generally healthy adults at a dose less than 10,000 IU/day. In a clinical study of healthy adults a 4,000 IU daily dose of vitamin D3 for up to five months was not associated with hypercalciuria or hypercalcaemia.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Bisphosphonates, combinations, ATC code: M05BB03.

ALENDRONATE SODIUM AND COLECALCIFEROL, MSD is a combination tablet containing the two active substances alendronate sodium trihydrate and colecalciferol (vitamin D3).

Alendronate
Alendronate sodium is a bisphosphonate that inhibits osteoclastic bone resorption with no direct effect on bone formation. Preclinical studies have shown preferential localisation of alendronate to sites of active resorption. Activity of osteoclasts is inhibited, but recruitment or attachment of osteoclasts is not affected. The bone formed during treatment with alendronate is of normal quality.

Colecalciferol (vitamin D3)
Vitamin D3 is produced in the skin by conversion of 7-dehydrocholesterol to vitamin D3 by ultraviolet light. In the absence of adequate sunlight exposure, vitamin D3 is an essential dietary nutrient. Vitamin D3 is converted to 25-hydroxyvitamin D3 in the liver, and stored until needed. Conversion to the active
calcium-mobilizing hormone 1,25-dihydroxyvitamin D₃ (calcitriol) in the kidney is tightly regulated. The principal action of 1,25-dihydroxyvitamin D₃ is to increase intestinal absorption of both calcium and phosphate as well as regulate serum calcium, renal calcium and phosphate excretion, bone formation and bone resorption.

Vitamin D₃ is required for normal bone formation. Vitamin D insufficiency develops when both sunlight exposure and dietary intake are inadequate. Insufficiency is associated with negative calcium balance, bone loss, and increased risk of skeletal fracture. In severe cases, deficiency results in secondary hyperparathyroidism, hypophosphataemia, proximal muscle weakness and osteomalacia, further increasing the risk of falls and fractures in osteoporotic individuals. Supplemental vitamin D reduces these risks and their consequences.

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

**ALENDRONATE SODIUM AND COLECALCIFEROL, MSD studies**

The effect of the lower dose of ALENDRONATE SODIUM AND COLECALCIFEROL, MSD (alendronate 70 mg/vitamin D₃ 2800 IU) on vitamin D status was demonstrated in a 15-week, multinational study that enrolled 682 osteoporotic post-menopausal women (serum 25-hydroxyvitamin D at baseline: mean, 56 nmol/l [22.3 ng/ml]; range, 22.5-225 nmol/l [9-90 ng/ml]). Patients received the lower strength (70 mg/2800 IU) of ALENDRONATE SODIUM AND COLECALCIFEROL, MSD (n=350) or FOSAMAX (alendronate) 70 mg (n=332) once a week; additional vitamin D supplements were prohibited. After 15 weeks of treatment, the mean serum 25-hydroxyvitamin D levels were significantly higher (26 %) in the ALENDRONATE SODIUM AND COLECALCIFEROL, MSD (70 mg/2800 IU) group (56 nmol/l [23 ng/ml]) than in the alendronate-only group (46 nmol/l [18.2 ng/ml]). The percentage of patients with vitamin D insufficiency (serum 25-hydroxyvitamin D < 37.5 nmol/l [< 15 ng/ml]) was significantly reduced by 62.5 % with ALENDRONATE SODIUM AND COLECALCIFEROL, MSD (70 mg/2800 IU) vs. alendronate-only (12 % vs. 32 %, respectively), through week 15. The percentage of patients with vitamin D deficiency (serum 25-hydroxyvitamin D < 22.5 nmol/l [< 9 ng/ml]) was significantly reduced by 92 % with ALENDRONATE SODIUM AND COLECALCIFEROL, MSD (70 mg/2800 IU) vs. alendronate-only (1 % vs 13 %, respectively). In this study, mean 25-hydroxyvitamin D levels in patients with vitamin D insufficiency at baseline (25-hydroxyvitamin D, 22.5 to 37.5 nmol/l [9 to < 15 ng/ml]) increased from 30 nmol/l (12.1 ng/ml) to 40 nmol/l (15.9 ng/ml) at week 15 in the ALENDRONATE SODIUM AND COLECALCIFEROL, MSD (70 mg/2800 IU) group (n=75) and decreased from 30 nmol/l (12.0 ng/ml) at baseline to 26 nmol/l (10.4 ng/ml) at week 15 in the alendronate-only group (n=70). There were no differences in mean serum calcium, phosphate, or 24-hour urine calcium between treatment groups.

The effect of the lower dose of ALENDRONATE SODIUM AND COLECALCIFEROL, MSD (alendronate 70 mg/vitamin D₃ 2800 IU) plus an additional 2800 IU Vitamin D₃ for a total of 5600 IU (the amount of vitamin D₃ in the higher dose of ALENDRONATE SODIUM AND COLECALCIFEROL, MSD) once weekly was demonstrated in a 24-week, extension study that enrolled 619 osteoporotic post-menopausal women. Patients in the Vitamin D₃ 2800 group received ALENDRONATE SODIUM AND COLECALCIFEROL, MSD (70 mg/2800 IU) (n=299) and patients in the Vitamin D₃ 5600 group received ALENDRONATE SODIUM AND COLECALCIFEROL, MSD (70 mg/2800 IU) plus an additional 2800 IU vitamin D₃ (n=309) once a week; additional vitamin D supplements were allowed. After 24-weeks of treatment, the mean serum 25-hydroxyvitamin D levels were significantly higher in the Vitamin D₃ 5600 group (69 nmol/l [27.6 ng/ml]) than in the Vitamin D₃ 2800 group (64 nmol/l [25.5 ng/ml]). The percentage of patients with vitamin D insufficiency was 5.4 % in the Vitamin D₃ 2800 group vs. 3.2 % in the Vitamin D₃ 5600 group through the 24-week extension. The percentage of patients with vitamin D deficiency was 0.3 % in the Vitamin D₃ 2800 group vs. zero in the Vitamin D₃ 5600 group. There were no differences in mean serum calcium, phosphate, or 24-hour urine calcium between treatment groups. The percentage of patients with hypercalciuria at the end of the 24-week extension was not statistically different between treatment groups.
Alendronate studies

The therapeutic equivalence of alendronate once weekly 70 mg (n=519) and alendronate 10 mg daily (n=370) was demonstrated in a one-year multicentre study of post-menopausal women with osteoporosis. The mean increases from baseline in lumbar spine BMD at one year were 5.1 % (95 % CI: 4.8, 5.4 %) in the 70 mg once-weekly group and 5.4 % (95 % CI: 5.0, 5.8 %) in the 10 mg daily group. The mean BMD increases were 2.3 % and 2.9 % at the femoral neck and 2.9 % and 3.1 % at the total hip in the 70 mg once weekly and 10 mg daily groups, respectively. The two treatment groups were also similar with regard to BMD increases at other skeletal sites.

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 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 (alendronate 3.2 % vs placebo 6.2 %) 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 %).

5.2. Pharmacokinetic properties

Alendronate

Absorption

Relative to an intravenous reference dose, the oral mean bioavailability of alendronate in women was 0.64 % for doses ranging from 5 to 70 mg when administered after an overnight fast and two hours before a standardised breakfast. 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.

The alendronate component in the ALENDRONATE SODIUM AND COLECALCIFEROL, MSD (70 mg/5600 IU) combination tablet is bioequivalent to the alendronate 70 mg tablet.

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 intravenous 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 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 [14C]alendronate, approximately 50 % of the radioactivity was excreted in the urine within 72 hours and little or no radioactivity was recovered in the faeces. Following a single 10 mg intravenous 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 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 anticipated to interfere with the excretion of other medicinal products by those systems in humans.

**Colecalciferol**

**Absorption**
In healthy adult subjects (males and females), following administration of ALENDRONATE SODIUM AND COLECALCIFEROL, MSD 70 mg/5600 IU after an overnight fast and two hours before a meal, the mean area under the serum-concentration-time curve (AUC0-80 hrs) for vitamin D3 (unadjusted for endogenous vitamin D3 levels) was 490.2 ng•hr/ml. The mean maximal serum concentration (Cmax) of vitamin D3 was 12.2 ng/ml and the median time to maximal serum concentration (Tmax) was 10.6 hours. The bioavailability of the 5600 IU vitamin D3 in ALENDRONATE SODIUM AND COLECALCIFEROL, MSD is similar to 5600 IU vitamin D3 administered alone.

**Distribution**
Following absorption, vitamin D3 enters the blood as part of chylomicrons. Vitamin D3 is rapidly distributed mostly to the liver where it undergoes metabolism to 25-hydroxyvitamin D3, the major storage form. Lesser amounts are distributed to adipose and muscle tissue and stored as vitamin D3 at these sites for later release into the circulation. Circulating vitamin D3 is bound to vitamin D-binding protein.

**Biotransformation**
Vitamin D3 is rapidly metabolized by hydroxylation in the liver to 25-hydroxyvitamin D3, and subsequently metabolized in the kidney to 1,25-dihydroxyvitamin D3, which represents the biologically active form. Further hydroxylation occurs prior to elimination. A small percentage of vitamin D3 undergoes glucuronidation prior to elimination.

**Elimination**
When radioactive vitamin D3 was administered to healthy subjects, the mean urinary excretion of radioactivity after 48 hours was 2.4 %, and the mean faecal excretion of radioactivity after 4 days was 4.9 %. In both cases, the excreted radioactivity was almost exclusively as metabolites of the parent. The mean half-life of vitamin D3 in the serum following an oral dose of ALENDRONATE SODIUM AND COLECALCIFEROL, MSD (70 mg/2800 IU) is approximately 24 hours.
Characteristics in patients

Preclinical studies show that alendronate 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 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).

5.3 Preclinical safety data

Non-clinical studies with the combination of alendronate and colecalciferol have not been conducted.

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 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.

Colecalciferol

At doses far higher than the human therapeutic range, reproductive toxicity has been observed in animal studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose (E460)
Lactose anhydrous
Medium chain triglycerides
Gelatin
Croscarmellose sodium
Sucrose
Colloidal silicon dioxide
Magnesium stearate (E572)
Butyl hydroxytoluene (E321)
Modified starch (maize)
Sodium aluminium silicate (E554)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months.

6.4 Special precautions for storage

Store in the original blister in order to protect from moisture and light.

6.5 Nature and contents of container

Wallet with sealed aluminium/aluminium blisters, in cartons containing 2 (1 wallet x 2 tablets), 4 (1 wallet x 4 tablets), 12 (3 wallets x 4 tablets) or 40 (10 wallets x 4 tablets) tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER(S)

Merck Sharp & Dohme Ltd.
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000 – 2 tablets
EU/0/00/000/000 – 4 tablets
EU/0/00/000/000 – 12 tablets
EU/0/00/000/000 – 40 tablets

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

10. DATE OF REVISION OF THE TEXT
ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION
A. MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

FROSST IBERICA, S.A.
Via Complutense, 140
ES-28805 Alcalá de Henares
Madrid, Spain

B. CONDITIONS OF THE MARKETING AUTHORISATION

• CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER

Medicinal product subject to medical prescription.

• CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Not applicable.

• OTHER CONDITIONS

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, as described in version 6 presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

Risk Management Plan

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 3 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted
• When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
• Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
• At the request of the EMEA

PSURs

The PSUR submission cycle based on the International Birth Date (IBD = 10 March 2005), until otherwise specified by the CHMP, will follow the PSUR cycle of the reference product.
ANNEX III

LABELLING AND PACKAGE LEAFLET
A. LABELLING
### 1. NAME OF THE MEDICINAL PRODUCT

ALENDRONATE SODIUM AND COLECALCIFEROL, MSD 70 mg/2800 IU tablets
Alendronic acid as alendronate sodium trihydrate/colecalciferol

### 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains:
70 mg alendronic acid as alendronate sodium trihydrate and 70 micrograms (2800 IU) colecalciferol (vitamin D₃).

### 3. LIST OF EXCIPIENTS

Also contains: lactose anhydrous and sucrose. See package leaflet for further information.

### 4. PHARMACEUTICAL FORM AND CONTENTS

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>2 tablets</td>
<td>4 tablets</td>
<td>6 tablets</td>
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<tr>
<td>12 tablets</td>
<td>40 tablets</td>
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### 5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use
To be taken once weekly, on the same day each week. Read the package leaflet before use.

### 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

### 7. OTHER SPECIAL WARNING(S), IF NECESSARY

Once weekly

### 8. EXPIRY DATE

EXP
9. SPECIAL STORAGE CONDITIONS

Store in the original blister in order to protect from moisture and light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Ltd.
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000 (2 tablets)
EU/0/00/000/000 (4 tablets)
EU/0/00/000/000 (6 tablets)
EU/0/00/000/000 (12 tablets)
EU/0/00/000/000 (40 tablets)

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ALENDRONATE SODIUM AND COLECALCIFEROL, MSD
70 mg
2800 IU
PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

IMMEDIATE PACKAGING – TRIFOLD PACK OF 2 or 4 TABLETS

1. NAME OF THE MEDICINAL PRODUCT

ALENDRONATE SODIUM AND COLECALCIFEROL, MSD 70 mg/2800 IU tablets
Alendronic acid as alendronate sodium trihydrate/colecalfierol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains:
70 mg alendronic acid as alendronate sodium trihydrate and 70 micrograms (2800 IU) colecalfierol (vitamin D₃).

3. LIST OF EXCIPIENTS

Also contains: lactose anhydrous and sucrose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

2 tablets
4 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.

Important information

How to take ALENDRONATE SODIUM AND COLECALCIFEROL, MSD tablets

1. **Take one tablet once a week.**
2. **Choose the day of the week that best fits your schedule.** When you get out of bed on the day you have chosen, and before taking your first food, drink or other medicines, swallow (do not chew or suck) one ALENDRONATE SODIUM AND COLECALCIFEROL, MSD tablet with a full glass of water (not mineral water).
3. **Continue your morning activities.** You can sit, stand or walk – just stay fully upright. Don’t lie down, eat, drink or take other medicines for at least 30 minutes. Do not lie down until after your first food of the day.
4. **Remember,** take ALENDRONATE SODIUM AND COLECALCIFEROL, MSD once each week on that same day for as long as your doctor prescribes it.

If you miss a dose, take only one ALENDRONATE SODIUM AND COLECALCIFEROL, MSD tablet on the morning after you remember. Do not take two tablets on the same day. Return to taking one tablet once a week, as originally scheduled on your chosen day.

There is important additional information about how to take ALENDRONATE SODIUM AND COLECALCIFEROL, MSD in the enclosed package leaflet. Please read it carefully.
Take one tablet once a week

Mark the day of the week that best fits your schedule:
MON     FRI
TUE     SAT
WED     SUN
THU

WEEK 1. Date: ____
WEEK 2. Date: ____
WEEK 3. Date: ____
WEEK 4. Date: ____

TIME TO REFILL

For your convenience, place a sticker on your calendar each week as a reminder to take your
ALENDRONATE SODIUM AND COLECALCIFEROL, MSD.

ALENDRONATE SODIUM AND COLECALCIFEROL, MSD
WEEK 1
ALENDRONATE SODIUM AND COLECALCIFEROL, MSD
WEEK 2
ALENDRONATE SODIUM AND COLECALCIFEROL, MSD
WEEK 3
ALENDRONATE SODIUM AND COLECALCIFEROL, MSD
WEEK 4
TIME TO REFILL

To remove, push tablets through from this side.
To remove, push tablets through from other side.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Once weekly

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original blister in order to protect from moisture and light.
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Ltd.
Hertford Road, Hoddlesdon
Hertfordshire EN11 9BU
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000 (2 tablets)
EU/0/00/000/000 (4 tablets)
EU/0/00/000/000 (6 tablets)
EU/0/00/000/000 (12 tablets)
EU/0/00/000/000 (40 tablets)

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

--
PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER PACKAGING – CARTON FOR 1, 3 or 10 TRIFOLD PACK OF 2 or 4 TABLETS

1. NAME OF THE MEDICINAL PRODUCT

ALENDRONATE SODIUM AND COLECALCIFEROL, MSD 70 mg/5600 IU tablets
Alendronic acid as alendronate sodium trihydrate/colecalciferol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains:
70 mg alendronic acid as alendronate sodium trihydrate and 140 micrograms (5600 IU) colecalciferol (vitamin D₃).

3. LIST OF EXCIPIENTS

Also contains: lactose anhydrous and sucrose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

2 tablets
4 tablets
12 tablets
40 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use
To be taken once weekly, on the same day each week. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Once weekly

8. EXPIRY DATE

EXP
9. SPECIAL STORAGE CONDITIONS

Store in the original blister in order to protect from moisture and light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Ltd.
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000 (2 tablets)
EU/0/00/000/000 (4 tablets)
EU/0/00/000/000 (12 tablets)
EU/0/00/000/000 (40 tablets)

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ALENDRONATE SODIUM AND COLECALCIFEROL, MSD
70 mg
5600 IU
PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

IMMEDIATE PACKAGING – TRIFOLD PACK OF 2 or 4 TABLETS

1. NAME OF THE MEDICINAL PRODUCT

ALENDRONATE SODIUM AND COLECALCIFEROL, MSD 70 mg/5600 IU tablets
Alendronic acid as alendronate sodium trihydrate/colecalciferol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains:
70 mg alendronic acid as alendronate sodium trihydrate and 140 micrograms (5600 IU) colecalciferol (vitamin D₃).

3. LIST OF EXCIPIENTS

Also contains: lactose anhydrous and sucrose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

2 tablets
4 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.

Important information

How to take ALENDRONATE SODIUM AND COLECALCIFEROL, MSD tablets

1. Take one tablet once a week.
2. Choose the day of the week that best fits your schedule. When you get out of bed on the day you have chosen, and before taking your first food, drink or other medicines, swallow (do not chew or suck) one ALENDRONATE SODIUM AND COLECALCIFEROL, MSD tablet with a full glass of water (not mineral water).
3. Continue your morning activities. You can sit, stand or walk – just stay fully upright. Don’t lie down, eat, drink or take other medicines for at least 30 minutes. Do not lie down until after your first food of the day.
4. Remember, take ALENDRONATE SODIUM AND COLECALCIFEROL, MSD once each week on that same day for as long as your doctor prescribes it.

If you miss a dose, take only one ALENDRONATE SODIUM AND COLECALCIFEROL, MSD tablet on the morning after you remember. Do not take two tablets on the same day. Return to taking one tablet once a week, as originally scheduled on your chosen day.

There is important additional information about how to take ALENDRONATE SODIUM AND COLECALCIFEROL, MSD in the enclosed package leaflet. Please read it carefully.
Take one tablet once a week

Mark the day of the week that best fits your schedule:
MON       FRI
TUE       SAT
WED       SUN
THU

WEEK 1. Date: ____
WEEK 2. Date: ____
WEEK 3. Date: ____
WEEK 4. Date: ____
TIME TO REFILL

For your convenience, place a sticker on your calendar each week as a reminder to take your
ALENDRONATE SODIUM AND COLECALCIFEROL, MSD.

ALENDRONATE SODIUM AND COLECALCIFEROL, MSD
WEEK 1
ALENDRONATE SODIUM AND COLECALCIFEROL, MSD
WEEK 2
ALENDRONATE SODIUM AND COLECALCIFEROL, MSD
WEEK 3
ALENDRONATE SODIUM AND COLECALCIFEROL, MSD
WEEK 4
TIME TO REFILL

To remove, push tablets through from this side.
To remove, push tablets through from other side.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT
OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Once weekly

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original blister in order to protect from moisture and light.
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Ltd.  
Hertford Road, Hoddesdon  
Hertfordshire EN11 9BU  
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000 (2 tablets)  
EU/0/00/000/000 (4 tablets)  
EU/0/00/000/000 (12 tablets)  
EU/0/00/000/000 (40 tablets)

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

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B. PACKAGE LEAFLET
Read all of this leaflet carefully before you start taking this medicine, even if this is a repeat prescription.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.
- It is particularly important to understand the information in section 3. HOW TO TAKE ALENDRONATE SODIUM AND COLECALCIFEROL, MSD, before taking this medicine.

In this leaflet:
1. What ALENDRONATE SODIUM AND COLECALCIFEROL, MSD is and what it is used for
2. Before you take ALENDRONATE SODIUM AND COLECALCIFEROL, MSD
3. How to take ALENDRONATE SODIUM AND COLECALCIFEROL, MSD
4. Possible side effects
5. How to store ALENDRONATE SODIUM AND COLECALCIFEROL, MSD
6. Further information

1. WHAT ALENDRONATE SODIUM AND COLECALCIFEROL, MSD IS AND WHAT IT IS USED FOR

What is ALENDRONATE SODIUM AND COLECALCIFEROL, MSD?
ALENDRONATE SODIUM AND COLECALCIFEROL, MSD is a tablet containing the two active substances, alendronate sodium trihydrate and colecalciferol known as vitamin D₃.

What is alendronate?
Alendronate belongs to a group of non-hormonal medicines called bisphosphonates. Alendronate prevents the loss of bone that occurs in women after they have been through the menopause, and helps to rebuild bone. It reduces the risk of spine and hip fractures.

What is vitamin D?
Vitamin D is an essential nutrient, required for calcium absorption and healthy bones. The body can only absorb calcium properly from our food if it has enough vitamin D. Very few foods contain vitamin D. The main source is through exposure to summer sunlight, which makes vitamin D in our skin. As we get older our skin makes less vitamin D. Too little vitamin D may lead to bone loss and osteoporosis. Severe vitamin D deficiency may cause muscle weakness which can lead to falls and a greater risk of fractures.

What is ALENDRONATE SODIUM AND COLECALCIFEROL, MSD used for?
Your doctor has prescribed ALENDRONATE SODIUM AND COLECALCIFEROL, MSD to treat your osteoporosis and because you are at risk of vitamin D insufficiency. ALENDRONATE SODIUM AND COLECALCIFEROL, MSD reduces the risk of spine and hip fractures.

ALENDRONATE SODIUM AND COLECALCIFEROL, MSD is a once weekly treatment.

What is osteoporosis?
Osteoporosis is a thinning and weakening of the bones. It is common in women after the menopause. At the menopause, the ovaries stop producing the female hormone, oestrogen, which helps to keep a
woman’s skeleton healthy. As a result, bone loss occurs and bones become weaker. The earlier a woman reaches the menopause, the greater the risk of osteoporosis.

Early on, osteoporosis usually has no symptoms. If left untreated, however, it can result in broken bones. Although these usually hurt, breaks in the bones of the spine may go unnoticed until they cause height loss. Broken bones can happen during normal, everyday activity, such as lifting, or from minor injury that would not generally break normal bone. Broken bones usually occur at the hip, spine, or wrist and can lead not only to pain but also to considerable problems like stooped posture (‘dowager’s hump’) and loss of mobility.

How can osteoporosis be treated?
Osteoporosis can be treated and it is never too late to begin treatment. ALENDRONATE SODIUM AND COLECALCIFEROL, MSD not only prevents the loss of bone but actually helps to rebuild bone you may have lost and reduces the risk of bones breaking in the spine and hip.

As well as your treatment with ALENDRONATE SODIUM AND COLECALCIFEROL, MSD, your doctor may suggest you make changes to your lifestyle to help your condition, such as:

Stopping smoking Smoking appears to increase the rate at which you lose bone and, therefore, may increase your risk of broken bones.

Exercise Like muscles, bones need exercise to stay strong and healthy. Consult your doctor before you begin any exercise programme.

Eating a balanced diet Your doctor can advise you about your diet or whether you should take any dietary supplements.

2. BEFORE YOU TAKE ALENDRONATE SODIUM AND COLECALCIFEROL, MSD

Do not take ALENDRONATE SODIUM AND COLECALCIFEROL, MSD
• if you are allergic (hypersensitive) to alendronate sodium trihydrate, colecalciferol or any of the other ingredients,
• if you have certain problems with your gullet (oesophagus - the tube that connects your mouth with your stomach) such as narrowing or difficulty swallowing,
• if you cannot stand or sit upright for at least 30 minutes,
• if your doctor has told you that you have low blood calcium.

If you think any of these apply to you, do not take the tablets. Talk to your doctor first and follow the advice given.

Take special care with ALENDRONATE SODIUM AND COLECALCIFEROL, MSD
It is important to tell your doctor before taking ALENDRONATE SODIUM AND COLECALCIFEROL, MSD
• if you suffer from kidney problems,
• if you have any allergies,
• if you have any swallowing or digestive problems,
• if you have low blood calcium levels,
• if you have cancer,
• if you are undergoing chemotherapy or radiotherapy,
• if you are taking steroids,
• if you don’t receive routine dental care,
• if you have gum disease,
• if you have a planned dental extraction.
Irritation, inflammation or ulceration of the gullet (oesophagus – the tube that connects your mouth with your stomach) often with symptoms of chest pain, heartburn, or difficulty or pain upon swallowing may occur, especially if patients do not drink a full glass of water and/or if they lie down less than 30 minutes after taking ALENDRONATE SODIUM AND COLECALCIFEROL, MSD. These side effects may worsen if patients continue to take ALENDRONATE SODIUM AND COLECALCIFEROL, MSD after developing these symptoms.

**Children and adolescents**
ALENDRONATE SODIUM AND COLECALCIFEROL, MSD should not be given to children and adolescents.

**Taking other medicines**
It is likely that calcium supplements, antacids, and some oral medicines will interfere with the absorption of ALENDRONATE SODIUM AND COLECALCIFEROL, MSD if taken at the same time. Therefore, it is important that you follow the advice given in section 3. HOW TO TAKE ALENDRONATE SODIUM AND COLECALCIFEROL, MSD.

It is likely that certain medicines or food additives may prevent the vitamin D in ALENDRONATE SODIUM AND COLECALCIFEROL, MSD from getting into your body, including artificial fat substitutes, mineral oils, orlistat and the cholesterol-lowering medicines, cholestyramine and colestipol. Medicines for fits (seizures) may decrease the effectiveness of vitamin D. Additional vitamin D supplements may be considered on an individual basis.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

**Taking ALENDRONATE SODIUM AND COLECALCIFEROL, MSD with food and drink**
It is likely that food and beverages (including mineral water) will make ALENDRONATE SODIUM AND COLECALCIFEROL, MSD less effective if taken at the same time. Therefore, it is important that you follow the advice given in section 3. HOW TO TAKE ALENDRONATE SODIUM AND COLECALCIFEROL, MSD.

**Pregnancy and breast-feeding**
ALENDRONATE SODIUM AND COLECALCIFEROL, MSD is only intended for use in postmenopausal women. You should not take ALENDRONATE SODIUM AND COLECALCIFEROL, MSD if you are or think you may be pregnant, or if you are breast-feeding.

**Driving and using machines**
There have been side effects reported with ALENDRONATE SODIUM AND COLECALCIFEROL, MSD that may affect your ability to drive or operate machinery. Individual responses to ALENDRONATE SODIUM AND COLECALCIFEROL, MSD may vary. (See POSSIBLE SIDE EFFECTS.)

**Important information about some of the ingredients of ALENDRONATE SODIUM AND COLECALCIFEROL, MSD**
ALENDRONATE SODIUM AND COLECALCIFEROL, MSD contains lactose and sucrose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. **HOW TO TAKE ALENDRONATE SODIUM AND COLECALCIFEROL, MSD**

Take one ALENDRONATE SODIUM AND COLECALCIFEROL, MSD tablet once a week.

Follow these instructions carefully to make sure you will benefit from ALENDRONATE SODIUM AND COLECALCIFEROL, MSD.
1) Choose the day of the week that best fits your schedule. Every week, take one ALENDRONATE SODIUM AND COLECALCIFEROL, MSD tablet on your chosen day.

*It is very important to follow instructions 2), 3), 4) and 5) to help the ALENDRONATE SODIUM AND COLECALCIFEROL, MSD tablet reach your stomach quickly and help reduce the chance of irritating your gullet (oesophagus - the tube that connects your mouth with your stomach).*

2) After getting up for the day and before taking any food, drink, or other medicine, swallow your ALENDRONATE SODIUM AND COLECALCIFEROL, MSD tablet whole with a full glass of water only (not mineral water) (not less than 200 ml or 7 fl. oz.).
- Do not take with mineral water (still or sparkling).
- Do not take with coffee or tea.
- Do not take with juice or milk.

Do not crush or chew the tablet or allow it to dissolve in your mouth.

3) Do not lie down — stay fully upright (sitting, standing or walking) — for at least 30 minutes after swallowing the tablet. Do not lie down until after your first food of the day.

4) Do not take ALENDRONATE SODIUM AND COLECALCIFEROL, MSD at bedtime or before getting up for the day.

5) If you develop difficulty or pain upon swallowing, chest pain, or new or worsening heartburn, stop taking ALENDRONATE SODIUM AND COLECALCIFEROL, MSD and contact your doctor.

6) After swallowing your ALENDRONATE SODIUM AND COLECALCIFEROL, MSD tablet, wait at least 30 minutes before taking your first food, drink, or other medicine of the day, including antacids, calcium supplements and vitamins. ALENDRONATE SODIUM AND COLECALCIFEROL, MSD is effective only if taken when your stomach is empty.

If you take more ALENDRONATE SODIUM AND COLECALCIFEROL, MSD than you should
If you take too many tablets by mistake, drink a full glass of milk and contact your doctor immediately. Do not make yourself vomit, and do not lie down.

If you forget to take ALENDRONATE SODIUM AND COLECALCIFEROL, MSD
If you miss a dose, just take one tablet on the morning after you remember. *Do not take two tablets on the same day*. Return to taking one tablet once a week, as originally scheduled on your chosen day.

If you stop taking ALENDRONATE SODIUM AND COLECALCIFEROL, MSD
It is important that you continue taking ALENDRONATE SODIUM AND COLECALCIFEROL, MSD for as long as your doctor prescribes the medicine. ALENDRONATE SODIUM AND COLECALCIFEROL, MSD can treat your osteoporosis only if you continue to take the tablets.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. **POSSIBLE SIDE EFFECTS**

Like all medicines, ALENDRONATE SODIUM AND COLECALCIFEROL, MSD can cause side effects, although not everybody gets them.

The following terms are used to describe how often side effects have been reported:
- Common (occurring in at least 1 of 100 patients and less than 1 of 10 patients treated).
- Uncommon (occurring in at least 1 of 1,000 patients and less than 1 of 100 patients treated).
- Rare (occurring in at least 1 of 10,000 patients and less than 1 of 1,000 patients treated).
Very rare (occurring in less than 1 of 10,000 patients treated).

Common:
- heartburn; difficulty swallowing; pain upon swallowing; ulceration of the gullet (oesophagus - the tube that connects your mouth with your stomach) which can cause chest pain, heartburn or difficulty or pain upon swallowing,
- bone, muscle and/or joint pain,
- abdominal pain; uncomfortable feeling in the stomach or belching after eating; constipation; full or bloated feeling in the stomach; diarrhoea; flatulence,
- headache.

Uncommon:
- nausea; vomiting,
- irritation or inflammation of the gullet (oesophagus – the tube that connects your mouth with your stomach),
- black or tar-like stools,
- rash; itching; redness of the skin.

Rare:
- allergic reactions such as hives; swelling of the face, lips, tongue and/or throat, possibly causing difficulty breathing or swallowing,
- symptoms of low blood calcium levels including muscle cramps or spasms and/or tingling sensation in the fingers or around the mouth,
- stomach or peptic ulcers (sometimes severe or with bleeding),
- narrowing of the gullet (oesophagus – the tube that connects your mouth with your stomach),
- blurred vision, pain or redness in the eye,
- rash made worse by sunlight,
- severe bone, muscle and/or joint pain,
- mouth ulcers when the tablets have been chewed or sucked,
- transient flu-like symptoms, such as aching muscles, generally feeling unwell and sometimes with fever usually at the start of treatment.

Very rare:
- severe skin reactions.

During post-marketing experience the following side effects have been reported (frequency not known):
- dizziness,
- changed sense of taste,
- joint swelling,
- tiredness,
- hair loss,
- jaw problems associated with delayed healing and infection, often following tooth extraction,
- swelling in the hands or legs,
- fracture of the thigh bone in patients on long-term treatment with ALENDRONATE SODIUM AND COLECICIFEROL, MSD. Thigh pain, weakness or discomfort may be an early indication of a possible fracture of the thigh bone.

Tell your doctor or pharmacist promptly about these or any other unusual symptoms.

It will help if you make a note of what you experienced, when it started and how long it lasted.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.
5. HOW TO STORE ALENDRONATE SODIUM AND COLECALCIFEROL, MSD

Keep out of the reach and sight of children.

Do not use ALENDRONATE SODIUM AND COLECALCIFEROL, MSD after the expiry date which is stated on the carton and the wallet after EXP. The expiry date refers to the last day of that month.

Store in the original blister in order to protect from moisture and light.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What ALENDRONATE SODIUM AND COLECALCIFEROL, MSD contains

The active substances are alendronate sodium trihydrate and colecalciferol (vitamin D₃). Each tablet contains 70 mg alendronic acid as alendronate sodium trihydrate and 70 micrograms (2800 IU) colecalciferol (vitamin D₃).

The other ingredients are microcrystalline cellulose (E460), lactose anhydrous, medium chain triglycerides, gelatin, croscarmellose sodium, sucrose, colloidal silicon dioxide, magnesium stearate (E572), butyl hydroxytoluene (E321), modified starch (maize), and sodium aluminium silicate (E554).

What ALENDRONATE SODIUM AND COLECALCIFEROL, MSD looks like and contents of the pack

ALENDRONATE SODIUM AND COLECALCIFEROL, MSD 70 mg/2800 IU tablets are available as capsule-shaped, white to off-white tablets marked with an outline of a bone image on one side and ‘710’ on the other.

The tablets are supplied in wallets with sealed aluminium blisters in cartons in the following pack sizes

- 2 tablets (1 wallet containing 2 tablets in aluminium blisters)
- 4 tablets (1 wallet containing 4 tablets in aluminium blisters)
- 6 tablets (3 wallets each containing 2 tablets in aluminium blisters).
- 12 tablets (3 wallets each containing 4 tablets in aluminium blisters).
- 40 tablets (10 wallets each containing 4 tablets in aluminium blisters).

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

Manufacturer
FROSST IBERICA, S.A.
Via Complutense, 140
E-28805 Alcalá de Henares
Madrid
Spain
For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last approved in
What is ALENDRONATE SODIUM AND COLECALCIFEROL, MSD?
ALENDRONATE SODIUM AND COLECALCIFEROL, MSD is a tablet containing the two active substances, alendronate sodium trihydrate and colecalciferol known as vitamin D₃.

What is alendronate?
Alendronate belongs to a group of non-hormonal medicines called bisphosphonates. Alendronate prevents the loss of bone that occurs in women after they have been through the menopause, and helps to rebuild bone. It reduces the risk of spine and hip fractures.

What is vitamin D?
Vitamin D is an essential nutrient, required for calcium absorption and healthy bones. The body can only absorb calcium properly from our food if it has enough vitamin D. Very few foods contain vitamin D. The main source is through exposure to summer sunlight, which makes vitamin D in our skin. As we get older our skin makes less vitamin D. Too little vitamin D may lead to bone loss and osteoporosis. Severe vitamin D deficiency may cause muscle weakness which can lead to falls and a greater risk of fractures.

What is ALENDRONATE SODIUM AND COLECALCIFEROL, MSD used for?
Your doctor has prescribed ALENDRONATE SODIUM AND COLECALCIFEROL, MSD to treat your osteoporosis and because you are at risk of vitamin D insufficiency. ALENDRONATE SODIUM AND COLECALCIFEROL, MSD reduces the risk of spine and hip fractures.

ALENDRONATE SODIUM AND COLECALCIFEROL, MSD is a once weekly treatment.

What is osteoporosis?
Osteoporosis is a thinning and weakening of the bones. It is common in women after the menopause. At the menopause, the ovaries stop producing the female hormone, oestrogen, which helps to keep a
woman’s skeleton healthy. As a result, bone loss occurs and bones become weaker. The earlier a woman reaches the menopause, the greater the risk of osteoporosis. Early on, osteoporosis usually has no symptoms. If left untreated, however, it can result in broken bones. Although these usually hurt, breaks in the bones of the spine may go unnoticed until they cause height loss. Broken bones can happen during normal, everyday activity, such as lifting, or from minor injury that would not generally break normal bone. Broken bones usually occur at the hip, spine, or wrist and can lead not only to pain but also to considerable problems like stooped posture (‘dowager’s hump’) and loss of mobility.

**How can osteoporosis be treated?**
Osteoporosis can be treated and it is never too late to begin treatment. ALENDRONATE SODIUM AND COLECALCIFEROL, MSD not only prevents the loss of bone but actually helps to rebuild bone you may have lost and reduces the risk of bones breaking in the spine and hip.

As well as your treatment with ALENDRONATE SODIUM AND COLECALCIFEROL, MSD, your doctor may suggest you make changes to your lifestyle to help your condition, such as:

- **Stopping smoking** Smoking appears to increase the rate at which you lose bone and, therefore, may increase your risk of broken bones.

- **Exercise** Like muscles, bones need exercise to stay strong and healthy. Consult your doctor before you begin any exercise programme.

- **Eating a balanced diet** Your doctor can advise you about your diet or whether you should take any dietary supplements.

2. **BEFORE YOU TAKE ALENDRONATE SODIUM AND COLECALCIFEROL, MSD**

**Do not take ALENDRONATE SODIUM AND COLECALCIFEROL, MSD**
- if you are allergic (hypersensitive) to alendronate sodium trihydrate, colecalciferol or any of the other ingredients,
- if you have certain problems with your gullet (oesophagus - the tube that connects your mouth, with your stomach) such as narrowing or difficulty swallowing,
- if you cannot stand or sit upright for at least 30 minutes,
- if your doctor has told you that you have low blood calcium.

If you think any of these apply to you, do not take the tablets. Talk to your doctor first and follow the advice given.

**Take special care with ALENDRONATE SODIUM AND COLECALCIFEROL, MSD**
It is important to tell your doctor before taking ALENDRONATE SODIUM AND COLECALCIFEROL, MSD
- if you suffer from kidney problems,
- if you have any allergies,
- if you have any swallowing or digestive problems,
- if you have low blood calcium levels,
- if you have cancer,
- if you are undergoing chemotherapy or radiotherapy,
- if you are taking steroids,
- if you don’t receive routine dental care,
- if you have gum disease,
- if you have a planned dental extraction.
Irritation, inflammation or ulceration of the gullet (oesophagus – the tube that connects your mouth with your stomach) often with symptoms of chest pain, heartburn, or difficulty or pain upon swallowing may occur, especially if patients do not drink a full glass of water and/or if they lie down less than 30 minutes after taking ALENDRONATE SODIUM AND COLECALCIFEROL, MSD. These side effects may worsen if patients continue to take ALENDRONATE SODIUM AND COLECALCIFEROL, MSD after developing these symptoms.

Children and adolescents
ALENDRONATE SODIUM AND COLECALCIFEROL, MSD should not be given to children and adolescents.

Taking other medicines
It is likely that calcium supplements, antacids, and some oral medicines will interfere with the absorption of ALENDRONATE SODIUM AND COLECALCIFEROL, MSD if taken at the same time. Therefore, it is important that you follow the advice given in section 3. HOW TO TAKE ALENDRONATE SODIUM AND COLECALCIFEROL, MSD.

It is likely that certain medicines or food additives may prevent the vitamin D in ALENDRONATE SODIUM AND COLECALCIFEROL, MSD from getting into your body, including artificial fat substitutes, mineral oils, orlistat and the cholesterol-lowering medicines, cholestyramine and colestipol. Medicines for fits (seizures) may decrease the effectiveness of vitamin D.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including vitamin D or medicines obtained without a prescription.

Taking ALENDRONATE SODIUM AND COLECALCIFEROL, MSD with food and drink
It is likely that food and beverages (including mineral water) will make ALENDRONATE SODIUM AND COLECALCIFEROL, MSD less effective if taken at the same time. Therefore, it is important that you follow the advice given in section 3. HOW TO TAKE ALENDRONATE SODIUM AND COLECALCIFEROL, MSD.

Pregnancy and breast-feeding
ALENDRONATE SODIUM AND COLECALCIFEROL, MSD is only intended for use in postmenopausal women. You should not take ALENDRONATE SODIUM AND COLECALCIFEROL, MSD if you are or think you may be pregnant, or if you are breast-feeding.

Driving and using machines
There have been side effects reported with ALENDRONATE SODIUM AND COLECALCIFEROL, MSD that may affect your ability to drive or operate machinery. Individual responses to ALENDRONATE SODIUM AND COLECALCIFEROL, MSD may vary. (See POSSIBLE SIDE EFFECTS.)

Important information about some of the ingredients of ALENDRONATE SODIUM AND COLECALCIFEROL, MSD
ALENDRONATE SODIUM AND COLECALCIFEROL, MSD contains lactose and sucrose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. HOW TO TAKE ALENDRONATE SODIUM AND COLECALCIFEROL, MSD
Take one ALENDRONATE SODIUM AND COLECALCIFEROL, MSD tablet once a week.

Follow these instructions carefully to make sure you will benefit from ALENDRONATE SODIUM AND COLECALCIFEROL, MSD.
1) Choose the day of the week that best fits your schedule. Every week, take one ALENDRONATE SODIUM AND COLECALCIFEROL, MSD tablet on your chosen day.

*It is very important to follow instructions 2), 3), 4) and 5) to help the ALENDRONATE SODIUM AND COLECALCIFEROL, MSD tablet reach your stomach quickly and help reduce the chance of irritating your gullet (oesophagus - the tube that connects your mouth with your stomach).*

2) After getting up for the day and before taking any food, drink, or other medicine, swallow your ALENDRONATE SODIUM AND COLECALCIFEROL, MSD tablet whole with a full glass of water only (not mineral water) (not less than 200 ml or 7 fl. oz.).

- Do not take with mineral water (still or sparkling).
- Do not take with coffee or tea.
- Do not take with juice or milk.

Do not crush or chew the tablet or allow it to dissolve in your mouth.

3) Do not lie down — stay fully upright (sitting, standing or walking) — for at least 30 minutes after swallowing the tablet. Do not lie down until after your first food of the day.

4) Do not take ALENDRONATE SODIUM AND COLECALCIFEROL, MSD at bedtime or before getting up for the day.

5) If you develop difficulty or pain upon swallowing, chest pain, or new or worsening heartburn, stop taking ALENDRONATE SODIUM AND COLECALCIFEROL, MSD and contact your doctor.

6) After swallowing your ALENDRONATE SODIUM AND COLECALCIFEROL, MSD tablet, wait at least 30 minutes before taking your first food, drink, or other medicine of the day, including antacids, calcium supplements and vitamins. ALENDRONATE SODIUM AND COLECALCIFEROL, MSD is effective only if taken when your stomach is empty.

**If you take more ALENDRONATE SODIUM AND COLECALCIFEROL, MSD than you should**
If you take too many tablets by mistake, drink a full glass of milk and contact your doctor immediately. Do not make yourself vomit, and do not lie down.

**If you forget to take ALENDRONATE SODIUM AND COLECALCIFEROL, MSD**
If you miss a dose, just take one tablet on the morning after you remember. Do not take two tablets on the same day. Return to taking one tablet once a week, as originally scheduled on your chosen day.

**If you stop taking ALENDRONATE SODIUM AND COLECALCIFEROL, MSD**
It is important that you continue taking ALENDRONATE SODIUM AND COLECALCIFEROL, MSD for as long as your doctor prescribes the medicine. ALENDRONATE SODIUM AND COLECALCIFEROL, MSD can treat your osteoporosis only if you continue to take the tablets.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

**4. POSSIBLE SIDE EFFECTS**

Like all medicines, ALENDRONATE SODIUM AND COLECALCIFEROL, MSD can cause side effects, although not everybody gets them.

The following terms are used to describe how often side effects have been reported:
Common (occurring in at least 1 of 100 patients and less than 1 of 10 patients treated).
Uncommon (occurring in at least 1 of 1,000 patients and less than 1 of 100 patients treated).
Rare (occurring in at least 1 of 10,000 patients and less than 1 of 1,000 patients treated).
Very rare (occurring in less than 1 of 10,000 patients treated).

Common:
• heartburn; difficulty swallowing; pain upon swallowing; ulceration of the gullet (oesophagus -
the tube that connects your mouth with your stomach) which can cause chest pain, heartburn or
difficulty or pain upon swallowing,
• bone, muscle and/or joint pain,
• abdominal pain; uncomfortable feeling in the stomach or belching after eating; constipation; full
or bloated feeling in the stomach; diarrhoea; flatulence,
• headache.

Uncommon:
• nausea; vomiting,
• irritation or inflammation of the gullet (oesophagus – the tube that connects your mouth with
your stomach) or stomach,
• black or tar-like stools,
• rash; itching; redness of the skin.

Rare:
• allergic reactions such as hives; swelling of the face, lips, tongue and/or throat, possibly causing
difficulty breathing or swallowing,
• symptoms of low blood calcium levels including muscle cramps or spasms and/or tingling
sensation in the fingers or around the mouth,
• stomach or peptic ulcers (sometimes severe or with bleeding),
• narrowing of the gullet (oesophagus – the tube that connects your mouth with your stomach),
• blurred vision, pain or redness in the eye,
• rash made worse by sunlight,
• severe bone, muscle and/or joint pain,
• mouth ulcers when the tablets have been chewed or sucked,
• transient flu-like symptoms, such as aching muscles, generally feeling unwell and sometimes
with fever usually at the start of treatment.

Very rare:
• severe skin reactions.

During post-marketing experience the following side effects have been reported (frequency not
known):
• dizziness,
• changed sense of taste,
• joint swelling,
• tiredness,
• hair loss,
• jaw problems associated with delayed healing and infection, often following tooth extraction,
• swelling in the hands or legs,
• fracture of the thigh bone in patients on long-term treatment with ALENDRONATE SODIUM
AND COLECALCIFEROL, MSD. Thigh pain, weakness or discomfort may be an early
indication of a possible fracture of the thigh bone.

Tell your doctor or pharmacist promptly about these or any other unusual symptoms.

It will help if you make a note of what you experienced, when it started and how long it lasted.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please
tell your doctor or pharmacist.
5. **HOW TO STORE ALENDRONATE SODIUM AND COLECALCIFEROL, MSD**

Keep out of the reach and sight of children.

Do not use ALENDRONATE SODIUM AND COLECALCIFEROL, MSD after the expiry date which is stated on the carton and the wallet after EXP. The expiry date refers to the last day of that month.

Store in the original blister in order to protect from moisture and light.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. **FURTHER INFORMATION**

**What ALENDRONATE SODIUM AND COLECALCIFEROL, MSD contains**

The active substances are alendronate sodium trihydrate and colecalciferol (vitamin D$_3$). Each tablet contains 70 mg alendronic acid as alendronate sodium trihydrate and 140 micrograms (5600 IU) colecalciferol (vitamin D$_3$).

The other ingredients are microcrystalline cellulose (E460), lactose anhydrous, medium chain triglycerides, gelatin, croscarmellose sodium, sucrose, colloidal silicon dioxide, magnesium stearate (E572), butylated hydroxytoluene (E321), modified starch (maize), and sodium aluminium silicate (E554).

**What ALENDRONATE SODIUM AND COLECALCIFEROL, MSD looks like and contents of the pack**

ALENDRONATE SODIUM AND COLECALCIFEROL, MSD 70 mg/5600 IU tablets are available as modified rectangle-shaped, white to off-white tablets marked with an outline of a bone image on one side and ‘270’ on the other.

The tablets are supplied in wallets with sealed aluminium blisters in cartons in the following pack sizes

- 2 tablets (1 wallet containing 2 tablets in aluminium blisters)
- 4 tablets (1 wallet containing 4 tablets in aluminium blisters)
- 12 tablets (3 wallets each containing 4 tablets in aluminium blisters).
- 40 tablets (10 wallets each containing 4 tablets in aluminium blisters).

Not all pack sizes may be marketed.

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