**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

ADROVANCE 70 mg/2,800 IU tablets
ADROVANCE 70 mg/5,600 IU tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ADROVANCE 70 mg/2,800 IU tablets
Each tablet contains 70 mg alendronic acid (as sodium trihydrate) and 70 micrograms (2,800 IU) colecalciferol (vitamin $D_3$).

*Excipients with known effect*
Each tablet contains 62 mg lactose (as lactose anhydrous) and 8 mg sucrose.

ADROVANCE 70 mg/5,600 IU tablets
Each tablet contains 70 mg alendronic acid (as sodium trihydrate) and 140 micrograms (5,600 IU) colecalciferol (vitamin $D_3$).

*Excipients with known effect*
Each tablet contains 63 mg lactose (as lactose anhydrous) and 16 mg sucrose.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Tablet

ADROVANCE 70 mg/2,800 IU tablets
Modified capsule-shaped, white to off-white tablets, marked with an outline of a bone image on one side, and '710' on the other.

ADROVANCE 70 mg/5,600 IU tablets
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

ADROVANCE is indicated for the treatment of postmenopausal osteoporosis in women at risk of vitamin D insufficiency. It reduces the risk of vertebral and hip fractures.

### 4.2 Posology and method of administration

Posology

The recommended dose is one tablet once weekly.

Patients should be instructed that if they miss a dose of ADROVANCE 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.

Due to the nature of the disease process in osteoporosis, ADROVANCE is intended for long-term use.

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

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.

ADROVANCE 70 mg/2,800 IU tablets
The equivalence of intake of 2,800 IU of vitamin $D_3$ weekly in ADROVANCE to daily dosing of vitamin D 400 IU has not been studied.

ADROVANCE 70 mg/5,600 IU tablets
The equivalence of intake of 5,600 IU of vitamin $D_3$ weekly in ADROVANCE to daily dosing of vitamin D 800 IU has not been studied.

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

*Renal impairment*
ADROVANCE is not recommended for patients with renal impairment where creatinine clearance is less than 35 ml/min, due to lack of experience. No dose adjustment is necessary for patients with a creatinine clearance greater than 35 ml/min.

*Paediatric population*
The safety and efficacy of ADROVANCE in children less than 18 years of age have not been established. This medicinal product should not be used in children less than 18 years of age because no data are available for the alendronic acid/colecalciferol combination. Currently available data for alendronic acid in the paediatric population is described in section 5.1.

Method of administration

Oral use.

To permit adequate absorption of alendronate:

ADROVANCE 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 sections 4.5 and 4.8).

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

- ADROVANCE should only be swallowed after getting up for the day with a full glass of water (not less than 200 ml).
- Patients should only swallow ADROVANCE whole. Patients should not crush or chew the tablet or allow the tablet to dissolve in their mouths because of a potential for oropharyngeal ulceration.
- Patients should not lie down for at least 30 minutes after taking ADROVANCE and until after the first food of the day.
- ADROVANCE should not be taken at bedtime or before arising for the day.

## 4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

- 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

*Upper gastrointestinal adverse reactions*
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). In patients with known Barrett's oesophagus, prescribers should consider the benefits and potential risks of alendronate on an individual patient basis.

Oesophageal reactions (sometimes severe and requiring hospitalisation), such as oesophagitis, oesophageal ulcers and oesophageal erosions, rarely followed by oesophageal stricture, have been reported in patients receiving alendronate. Physicians should therefore be alert to any signs or symptoms signalling a possible oesophageal reaction and patients should be instructed to discontinue alendronate and seek medical attention if they develop symptoms of oesophageal irritation such as dysphagia, pain on swallowing or retrosternal pain 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*
Osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection (including osteomyelitis), has been reported in patients with cancer who are receiving treatment regimens including primarily intravenously administered bisphosphonates. Many of these patients were also receiving chemotherapy and corticosteroids. Osteonecrosis of the jaw has also been reported in patients with osteoporosis receiving oral bisphosphonates.

The following risk factors should be considered when evaluating an individual's risk of developing osteonecrosis of the jaw:
- potency of the bisphosphonate (highest for zoledronic acid), route of administration (see above) and cumulative dose
- cancer, chemotherapy, radiotherapy, corticosteroids, angiogenesis inhibitors, smoking
- a history of dental disease, poor oral hygiene, periodontal disease, invasive dental procedures and poorly fitting dentures

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

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

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

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

*Musculoskeletal pain*
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.

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

*Atypical fractures of other bones*
Atypical fractures of other bones, such as the ulna and tibia have also been reported in patients receiving long-term treatment. As with atypical femoral fractures, these fractures occur after minimal, or no trauma and some patients experience prodromal pain prior to presenting with a completed fracture. In cases of ulna fracture, this may be associated with repetitive stress loading associated with the long-term use of walking aids.

*Renal impairment*
ADROVANCE is not recommended for patients with renal impairment where creatinine clearance is less than 35 ml/min (see section 4.2).

*Bone and mineral metabolism*
Causes of osteoporosis other than oestrogen deficiency and ageing should be considered.

Hypocalcaemia must be corrected before initiating therapy with ADROVANCE (see section 4.3). Other disorders affecting mineral metabolism (such as vitamin D deficiency and hypoparathyroidism) should also be effectively treated before starting this medicinal product. The content of vitamin D in ADROVANCE 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 ADROVANCE.

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 $D_3$ 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 $D_3$.

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

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

## 4.5 Interaction with other medicinal products and other forms of interaction

Alendronate
If taken at the same time, it is likely that food and beverages (including mineral water), calcium supplements, antacids, and some oral medicinal products will interfere with absorption of alendronate. Therefore, patients must wait at least 30 minutes after taking alendronate before taking any other oral medicinal product (see sections 4.2 and 5.2).

Since Non Steroidal Anti-Inflammatory Drug (NSAID) use is associated with gastrointestinal irritation, caution should be used during concomitant use with alendronate.

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 Fertility, pregnancy and lactation

ADROVANCE is only intended for use in postmenopausal women and therefore it should not be used during pregnancy or in breast-feeding women.

Pregnancy
There are no or limited amount of data from the use of alendronate in pregnant women. Studies in animals have shown reproductive toxicity. Alendronate given during pregnancy in rats caused dystocia related to hypocalcaemia (see section 5.3). Studies in animals have shown hypercalcaemia and reproductive toxicity with high doses of vitamin D (see section 5.3). ADROVANCE should not be used during pregnancy.

Breast-feeding
It is unknown whether alendronate/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. Colecalciferol and some of its active metabolites pass into breast milk. ADROVANCE should not be used during breast-feeding.

Fertility
Bisphosphonates are incorporated into the bone matrix, from which they are gradually released over a period of years. The amount of bisphosphonate incorporated into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the dose and duration of bisphosphonate use (see section 5.2). There are no data on foetal risk in humans. However, there is a theoretical risk of foetal harm, predominantly skeletal, if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on the risk has not been studied.

## 4.7 Effects on ability to drive and use machines

ADROVANCE has no or negligible direct influence on the ability to drive and use machines. Patients may experience certain adverse reactions (for example blurred vision, dizziness and severe bone muscle or joint pain (see section 4.8)) that may influence the ability to drive and use machines.

## 4.8 Undesirable effects

Summary of the safety profile
The most commonly reported adverse reactions are upper gastrointestinal adverse reactions including abdominal pain, dyspepsia, oesophageal ulcer, dysphagia, abdominal distension and acid regurgitation (> 1 %).

Tabulated list of adverse reactions
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 the combination of alendronate and colecalciferol.

Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), not known (cannot be estimated from the available data).

| System organ class | Frequency | Adverse reactions |
|---|---|---|
| ***Immune system disorders*** | Rare | hypersensitivity reactions including urticaria and angioedema |
| ***Metabolism and nutrition disorders*** | Rare | symptomatic hypocalcaemia, often in association with predisposing conditions[§] |
| ***Nervous system disorders*** | Common | headache, dizziness[†] |
| | Uncommon | dysgeusia[†] |
| ***Eye disorders*** | Uncommon | eye inflammation (uveitis, scleritis, or episcleritis) |
| ***Ear and labyrinth disorders*** | Common | vertigo[†] |
| | Very rare | osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction) |
| ***Gastrointestinal disorders*** | Common | abdominal pain, dyspepsia, constipation, diarrhoea, flatulence, oesophageal ulcer*, dysphagia*, abdominal distension, acid regurgitation |
| | Uncommon | nausea, vomiting, gastritis, oesophagitis*, oesophageal erosions*, melena[†] |
| | Rare | oesophageal stricture*, oropharyngeal ulceration*, upper gastrointestinal PUBs (perforation, ulcers, bleeding)[§] |
| ***Skin and subcutaneous tissue disorders*** | Common | alopecia[†], pruritus[†] |
| | Uncommon | rash, erythema |
| | Rare | rash with photosensitivity, severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis[‡] |
| ***Musculoskeletal and connective tissue disorders*** | Very common | musculoskeletal (bone, muscle or joint) pain which is sometimes severe[†§] |
| | Common | joint swelling[†] |
| | Rare | osteonecrosis of the jaw[‡§], atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction) |
| | Not known | atypical fractures of other bones |
| ***General disorders and administration site conditions*** | Common | asthenia[†], peripheral oedema[†] |
| | Uncommon | transient symptoms as in an acute-phase response (myalgia, malaise and rarely, fever), typically in association with initiation of treatment[†] |

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

Description of selected adverse reactions

*Atypical subtrochanteric and diaphyseal femoral fractures*
Although the pathophysiology is uncertain, consistent evidence from epidemiological studies suggests an increased risk of atypical subtrochanteric and diaphyseal femoral fractures with long-term bisphosphonate therapy for postmenopausal osteoporosis, particularly beyond three to five years of use. The absolute risk of atypical subtrochanteric and diaphyseal long bone fractures (bisphosphonate class adverse reaction) remains rare.

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

## 4.9 Overdose

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

*Management*
No specific information is available on the treatment of overdose with alendronate. In case of overdose with ADROVANCE, 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 $D_3$ for up to five months was not associated with hypercalciuria or hypercalcaemia.

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for treatment of bone diseases, Bisphosphonates, combinations, ATC code: M05BB03

Mechanism of action

*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 $D_3$)*
Vitamin $D_3$ is produced in the skin by conversion of 7-dehydrocholesterol to vitamin $D_3$ by ultraviolet light. In the absence of adequate sunlight exposure, vitamin $D_3$ is an essential dietary nutrient. Vitamin $D_3$ is converted to 25-hydroxyvitamin $D_3$ in the liver, and stored until needed. Conversion to the active calcium-mobilising hormone 1,25-dihydroxyvitamin $D_3$ (calcitriol) in the kidney is tightly regulated. The principal action of 1,25-dihydroxyvitamin $D_3$ 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 $D_3$ 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.

Clinical efficacy and safety

*ADROVANCE studies*
The effect of the lower dose of ADROVANCE (alendronate 70 mg/vitamin $D_3$ 2,800 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/2,800 IU) of ADROVANCE (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 ADROVANCE (70 mg/2,800 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 ADROVANCE (70 mg/2,800 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 ADROVANCE (70 mg/2,800 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 ADROVANCE (70 mg/2,800 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 ADROVANCE (alendronate 70 mg/vitamin $D_3$ 2,800 IU) plus an additional 2,800 IU Vitamin $D_3$ for a total of 5,600 IU (the amount of vitamin $D_3$ in the higher dose of ADROVANCE) once weekly was demonstrated in a 24-week, extension study that enrolled 619 osteoporotic post-menopausal women. Patients in the Vitamin $D_3$ 2,800 group received ADROVANCE (70 mg/2,800 IU) (n=299) and patients in the Vitamin $D_3$ 5,600 group received ADROVANCE (70 mg/2,800 IU) plus an additional 2,800 IU vitamin $D_3$ (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 $D_3$ 5,600 group (69 nmol/l [27.6 ng/ml]) than in the Vitamin $D_3$ 2,800 group (64 nmol/l [25.5 ng/ml]). The percentage of patients with vitamin D insufficiency was 5.4 % in the Vitamin $D_3$ 2,800 group vs. 3.2 % in the Vitamin $D_3$ 5,600 group through the 24-week extension. The percentage of patients with vitamin D deficiency was 0.3 % in the Vitamin $D_3$ 2,800 group vs. zero in the Vitamin $D_3$ 5,600 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 %).

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

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

## 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 ADROVANCE (70 mg/2,800 IU) combination tablet and the ADROVANCE (70 mg/5,600 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 [$^{14}$C]alendronate, approximately 50 % of the radioactivity was excreted in the urine within 72 hours and little or no radioactivity was recovered in the faeces. Following a single 10 mg 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 ADROVANCE 70 mg/2,800 IU tablets after an overnight fast and two hours before a meal, the mean area under the serum-concentration-time curve ($AUC_{0\text{-}120\ hrs}$) for vitamin $D_3$ (unadjusted for endogenous vitamin $D_3$ levels) was 296.4 ng•hr/ml. The mean maximal serum concentration ($C_{max}$) of vitamin $D_3$ was 5.9 ng/ml, and the median time to maximal serum concentration ($T_{max}$) was 12 hours. The bioavailability of the 2,800 IU vitamin $D_3$ in ADROVANCE is similar to 2,800 IU vitamin $D_3$ administered alone.

In healthy adult subjects (males and females), following administration of ADROVANCE 70 mg/5,600 IU after an overnight fast and two hours before a meal, the mean area under the serum-concentration-time curve ($AUC_{0\text{-}80\ hrs}$) for vitamin $D_3$ (unadjusted for endogenous vitamin $D_3$ levels) was 490.2 ng•hr/ml. The mean maximal serum concentration ($C_{max}$) of vitamin $D_3$ was 12.2 ng/ml and the median time to maximal serum concentration ($T_{max}$) was 10.6 hours. The bioavailability of the 5,600 IU vitamin $D_3$ in ADROVANCE is similar to 5,600 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 metabolised by hydroxylation in the liver to 25-hydroxyvitamin $D_3$, and subsequently metabolised 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 ADROVANCE (70 mg/2,800 IU) is approximately 24 hours.

*Renal impairment*
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)
Butylhydroxytoluene (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

ADROVANCE 70 mg/2,800 IU tablets
Aluminium/aluminium blisters, in cartons containing 2, 4, 6 or 12 tablets.

ADROVANCE 70 mg/5,600 IU tablets
Aluminium/aluminium blisters, in cartons containing 2, 4 or 12 tablets.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

No special requirements.

## 7. MARKETING AUTHORISATION HOLDER(S)

N.V. Organon
Kloosterstraat 6
5349 AB Oss
The Netherlands

## 8. MARKETING AUTHORISATION NUMBER(S)

ADROVANCE 70 mg/2,800 IU tablets
EU/1/06/364/001 – 2 tablets
EU/1/06/364/002 – 4 tablets
EU/1/06/364/003 – 6 tablets
EU/1/06/364/004 – 12 tablets

ADROVANCE 70 mg/5,600 IU tablets
EU/1/06/364/006 – 2 tablets
EU/1/06/364/007 – 4 tablets
EU/1/06/364/008 – 12 tablets

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: 4 January 2007
Date of latest renewal: 21 November 2011

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

# ANNEX II

**A. MANUACTURER(S) RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

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

Merck Sharp & Dohme BV
Waarderweg 39
2031 BN, Haarlem
The Netherlands

Organon Heist bv
Industriepark 30
2220 Heist-op-den-Berg
Belgium

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

## C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

# A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**
**CARTON FOR ADROVANCE 70 mg/2,800 IU**

## 1. NAME OF THE MEDICINAL PRODUCT

ADROVANCE 70 mg/2,800 IU tablets
alendronic acid/colecalciferol

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 70 mg alendronic acid (as sodium trihydrate) and 70 micrograms (2,800 IU) colecalciferol (vitamin $D_3$).

## 3. LIST OF EXCIPIENTS

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

## 4. PHARMACEUTICAL FORM AND CONTENTS

2 tablets
4 tablets
6 tablets
12 tablets

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Once weekly.
For oral use.

**Take one tablet once a week**

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

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

Keep out of the sight and reach of children.

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

## 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

N.V. Organon
Kloosterstraat 6
5349 AB Oss
The Netherlands

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/364/001 (2 tablets)
EU/1/06/364/002 (4 tablets)
EU/1/06/364/003 (6 tablets)
EU/1/06/364/004 (12 tablets)

## 13. BATCH NUMBER

Batch

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

ADROVANCE
70 mg
2,800 IU

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER FOR ADROVANCE 70 mg/2,800 IU**

## 1. NAME OF THE MEDICINAL PRODUCT

ADROVANCE 70 mg/2,800 IU tablets
alendronic acid/colecalciferol

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Organon

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**
**CARTON FOR ADROVANCE 70 mg/5,600 IU**

## 1. NAME OF THE MEDICINAL PRODUCT

ADROVANCE 70 mg/5,600 IU tablets
alendronic acid/colecalciferol

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 70 mg alendronic acid (as sodium trihydrate) and 140 micrograms (5,600 IU) colecalciferol (vitamin $D_3$).

## 3. LIST OF EXCIPIENTS

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

## 4. PHARMACEUTICAL FORM AND CONTENTS

2 tablets
4 tablets
12 tablets

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Once weekly.
For oral use.

**Take one tablet once a week**

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

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

Keep out of the sight and reach of children.

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

## 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

N.V. Organon
Kloosterstraat 6
5349 AB Oss
The Netherlands

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/364/006 (2 tablets)
EU/1/06/364/007 (4 tablets)
EU/1/06/364/008 (12 tablets)

## 13. BATCH NUMBER

Batch

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

ADROVANCE
70 mg
5,600 IU

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC

SN
NN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER FOR ADROVANCE 70 mg/5,600 IU**

## 1. NAME OF THE MEDICINAL PRODUCT

ADROVANCE 70 mg/5,600 IU tablets
alendronic acid/colecalciferol

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Organon

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

**PARTICULARS TO APPEAR WITHIN THE OUTER PACKAGING (CARTON)**

**Instruction Card**

**Important information**

**How to take ADROVANCE 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 crush or chew the tablet or allow it to dissolve in your mouth) one **ADROVANCE** 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 **ADROVANCE once** each week on that same day for as long as your doctor prescribes it.

**If you miss a dose**, take only one **ADROVANCE** 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 **ADROVANCE** in the package leaflet. Please read it carefully.

**B. PACKAGE LEAFLET**

**Package leaflet: Information for the user**

**ADROVANCE 70 mg/2,800 IU tablets**
**ADROVANCE 70 mg/5,600 IU tablets**
alendronic acid/colecalciferol

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**
- 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 only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.
- It is particularly important to understand the information in section 3 before taking this medicine.

**What is in this leaflet**



## 1. What ADROVANCE is and what it is used for

**What is ADROVANCE?**
ADROVANCE is a tablet containing the two active substances, alendronic acid (commonly called alendronate) and colecalciferol known as vitamin $D_3$.

**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 ADROVANCE used for?**
Your doctor has prescribed ADROVANCE to treat your osteoporosis and because you are at risk of vitamin D insufficiency. It reduces the risk of spine and hip fractures in women after menopause.

**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?**
As well as your treatment with ADROVANCE, 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. What you need to know before you take ADROVANCE

**Do not take ADROVANCE**
- if you are allergic to alendronic acid, colecalciferol or any of the other ingredients of this medicine (listed in section 6),
- 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.

**Warnings and precautions**
Talk to your doctor or pharmacist before taking ADROVANCE if:
- you suffer from kidney problems,
- you have, or have recently had, any swallowing or digestive problems,
- your doctor has told you that you have Barrett's oesophagus (a condition associated with changes in the cells that line the lower oesophagus),
- you have been told you have trouble absorbing minerals in your stomach or intestines (malabsorption syndrome),
- you have poor dental health, gum disease, a planned dental extraction or you don't receive routine dental care,
- you have cancer,
- you are undergoing chemotherapy or radiotherapy,
- you are taking angiogenesis inhibitors (such as bevacizumab, or thalidomide) which are used in the treatment of cancer,
- you are taking corticosteroids (such as prednisone or dexamethasone) which are used in the treatment of such conditions as asthma, rheumatoid arthritis, and severe allergies,
- you are or have been a smoker (as this may increase the risk of dental problems).

You may be advised to have a dental check-up before starting treatment with ADROVANCE.

It is important to maintain good oral hygiene when being treated with ADROVANCE. You should have routine dental check-ups throughout your treatment and you should contact your doctor or dentist if you experience any problems with your mouth or teeth such as loose teeth, pain or swelling.

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 ADROVANCE. These side effects may worsen if patients continue to take ADROVANCE after developing these symptoms.

**Children and adolescents**
ADROVANCE should not be given to children and adolescents less than 18 years of age.

**Other medicines and ADROVANCE**
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

It is likely that calcium supplements, antacids, and some oral medicines will interfere with the absorption of ADROVANCE if taken at the same time. Therefore, it is important that you follow the advice given in section 3 and wait at least 30 minutes before taking any other oral medicines or supplements.

Certain medicines for rheumatism or long-term pain called NSAIDs (e.g. acetylsalicylic acid or ibuprofen) might cause digestive problems. Therefore, caution should be used when these medicines are taken at the same time as ADROVANCE.

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

**ADROVANCE with food and drink**
It is likely that food and beverages (including mineral water) will make ADROVANCE less effective if taken at the same time. Therefore, it is important that you follow the advice given in section 3. You must wait at least 30 minutes before taking any food and beverages except water.

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

**Driving and using machines**
There have been side effects (for example blurred vision, dizziness and severe bone, muscle or joint pain) reported with ADROVANCE that may affect your ability to drive or operate machinery (see section 4). If you experience any of these side effects you should not drive until you feel better.

**ADROVANCE 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.

**ADROVANCE contains sodium.**
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

## 3. How to take ADROVANCE

Always take ADROVANCE exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

**Take one ADROVANCE tablet <u>once a week</u>.**

Follow these instructions carefully.

1) Choose the day of the week that best fits your schedule. Every week, take one ADROVANCE tablet on your chosen day.

It is very important to follow instructions 2), 3), 4) and 5) to help the ADROVANCE 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 ADROVANCE tablet whole with a full glass of water only (not mineral water) (not less than 200 ml), so that ADROVANCE is adequately absorbed.

- 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 because of the possibility of mouth ulceration.

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 ADROVANCE 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 ADROVANCE and contact your doctor.

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

**If you take more ADROVANCE 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 ADROVANCE**
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 ADROVANCE**
It is important that you take ADROVANCE for as long as your doctor prescribes the medicine. Since it is not known how long you should take ADROVANCE, you should discuss the need to stay on this medicine with your doctor periodically to determine if ADROVANCE is still right for you.

An Instruction Card is included in the carton for ADROVANCE. It contains important information reminding you how to take ADROVANCE properly.

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

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**See your doctor immediately** if you notice any of the following side effects, which may be serious, and for which you may need urgent medical treatment:
Common (may affect up to 1 in 10 people):
- 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.

Rare (may affect up to 1 in 1,000 people):
- allergic reactions such as hives; swelling of the face, lips, tongue and/or throat, possibly causing difficulty breathing or swallowing; severe skin reactions,
- pain in the mouth, and/or jaw, swelling or sores inside the mouth, numbness or a feeling of heaviness in the jaw, or loosening of a tooth. These could be signs of bone damage in the jaw (osteonecrosis) generally associated with delayed healing and infection, often following tooth extraction. Contact your doctor and dentist if you experience such symptoms,
- unusual fracture of the thigh bone particularly in patients on long-term treatment for osteoporosis may occur rarely. Contact your doctor if you experience pain, weakness or discomfort in your thigh, hip or groin as this may be an early indication of a possible fracture of the thigh bone,
- bone, muscle and/or joint pain which is severe.

Not known (cannot be estimated from the available data):
- unusual fracture in locations other than thigh bone.

**Other side effects include**
Very common (may affect more than 1 in 10 people):
- bone, muscle and/or joint pain which is sometimes severe.

Common (may affect up to 1 in 10 people):
- joint swelling,
- abdominal pain; uncomfortable feeling in the stomach or belching after eating; constipation; full or bloated feeling in the stomach; diarrhoea; flatulence,
- hair loss; itching,
- headache; dizziness,
- tiredness; swelling in the hands or legs.

Uncommon (may affect up to 1 in 100 people):
- 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,
- blurred vision; pain or redness in the eye,
- rash; redness of the skin,
- transient flu-like symptoms, such as aching muscles, generally feeling unwell and sometimes with fever usually at the start of treatment,
- taste disturbance.

Rare (may affect up to 1 in 1,000 people):
- 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),
- rash made worse by sunlight,
- mouth ulcers.

Very rare (may affect up to 1 in 10,000 people):
- talk to your doctor if you have ear pain, discharge from the ear, and/or an ear infection. These could be signs of bone damage in the ear.

**Reporting of side effects**
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store ADROVANCE

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the blister 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.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

**What ADROVANCE contains**

The active substances are alendronic acid and colecalciferol (vitamin $D_3$). Each ADROVANCE 70 mg/2,800 IU tablet contains 70 mg alendronic acid (as sodium trihydrate) and 70 micrograms (2,800 IU) colecalciferol (vitamin $D_3$). Each ADROVANCE 70 mg/5,600 IU tablet contains 70 mg alendronic acid (as sodium trihydrate) and 140 micrograms (5,600 IU) colecalciferol (vitamin $D_3$).

The other ingredients are microcrystalline cellulose (E460), lactose anhydrous (see section 2), medium chain triglycerides, gelatin, croscarmellose sodium, sucrose (see section 2), colloidal silicon dioxide, magnesium stearate (E572), butylhydroxytoluene (E321), modified starch (maize), and sodium aluminium silicate (E554).

**What ADROVANCE looks like and contents of the pack**

ADROVANCE 70 mg/2,800 IU tablets are available as modified capsule-shaped, white to off-white tablets marked with an outline of a bone image on one side and ‘710’ on the other. ADROVANCE 70 mg/2,800 IU tablets are available in packs containing 2, 4, 6 or 12 tablets.

ADROVANCE 70 mg/5,600 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. ADROVANCE 70 mg/5,600 IU tablets are available in packs containing 2, 4 or 12 tablets.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder**
N.V. Organon
Kloosterstraat 6
5349 AB Oss
The Netherlands

**Manufacturer**
Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

Organon Heist bv
Industriepark 30
2220 Heist-op-den-Berg
Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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