ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

VANTAVO 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 D_3).

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

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

4.2 Posology and method of administration

Posology

The recommended dose is one VANTAVO tablet once weekly.

Patients should be instructed that if they miss a dose of VANTAVO 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, VANTAVO 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 VANTAVO 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. The equivalence of intake of 2800 IU of vitamin D_3 weekly in VANTAVO to daily dosing of vitamin D 400 IU has not been studied.

Elderly population:
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:
VANTAVO is not recommended for patients with renal impairment where GFR is less than 35 ml/min, due to lack of experience. No dose adjustment is necessary for patients with a glomerular filtration rate (GFR) greater than 35 ml/min.

Paediatric population:
The safety and efficacy of VANTAVO in children less than 18 years of age has not been established. VANTAVO should not be used in children less than 18 years of age because no data are available.

Method of administration

Oral use.

To permit adequate absorption of alendronate:

VANTAVO 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):

- VANTAVO 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 VANTAVO 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.
- Patients should not lie down for at least 30 minutes after taking VANTAVO.
- VANTAVO 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.
- 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, 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.

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.

Renal insufficiency
VANTAVO is not recommended for patients with renal impairment where GFR 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 VANTAVO (see section 4.3). Other disorders affecting mineral metabolism (such as vitamin D deficiency and hypoparathyroidism) should also be effectively treated before starting VANTAVO. The content of vitamin D in VANTAVO 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 VANTAVO.

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, 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).

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

VANTAVO 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 adequate data from the use of VANTAVO 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).

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

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 fetal risk in humans. However, there is a theoretical risk of fetal harm, predominantly skeletal, if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on the risk has not been studied.

4.7 Effects on ability to drive and use machines

Certain adverse reactions that have been reported with VANTAVO may affect some patients' ability to drive or operate machinery. Individual responses to VANTAVO may vary (see section 4.8).

4.8 Undesirable effects

The most commonly reported adverse reactions are upper gastrointestinal adverse reactions including abdominal pain, dyspepsia, oesophageal ulcer, dysphagia, abdominal distension and acid regurgitation ($\geq 1/100$ to $< 1/10$).

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 VANTAVO.

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)

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[†]
Gastrointestinal disorders:	*Common:* abdominal pain, dyspepsia, constipation, diarrhoea, flatulence, oesophageal ulcer*, dysphagia*, abdominal distension, acid regurgitation *Uncommon:* nausea, vomiting, gastritis, oesophagitis*, oesophageal erosions*, melena[†] *Rare:* oesophageal stricture*, oropharyngeal ulceration*, upper gastrointestinal PUBs (perforation, ulcers, bleeding)[§]
Skin and subcutaneous tissue disorders:	*Common:* alopecia[†], pruritus[†] *Uncommon:* rash, erythema *Rare:* rash with photosensitivity, severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis[‡]
Musculoskeletal and connective tissue disorders:	*Very common:* musculoskeletal (bone, muscle or joint) pain which is sometimes severe[†§] *Common:* joint swelling[†] *Rare:* osteonecrosis of the jaw[‡§]; atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction)[⊥]
General disorders and administration site conditions:	*Common:* asthenia[†], peripheral oedema[†] *Uncommon:* transient symptoms as in an acute-phase response (myalgia, malaise and rarely, fever), typically in association with initiation of treatment[†]

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

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 VANTAVO, 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

VANTAVO is a combination tablet containing the two active substances alendronate sodium trihydrate and colecalciferol (vitamin D_3).

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-mobilizing 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.

VANTAVO studies
The effect of VANTAVO (alendronate 70 mg/vitamin D_3 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 VANTAVO (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 VANTAVO (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 VANTAVO (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 VANTAVO (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 VANTAVO (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 ≥ 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.

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 VANTAVO (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 [^{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 VANTAVO 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 2800 IU vitamin D_3 in VANTAVO 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 VANTAVO (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
Silica, colloidal anhydrous
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 4tablets) 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/1/09/572/001 – 2 tablets
EU/1/09/572/002 – 4 tablets
EU/1/09/572/003 – 6 tablets
EU/1/09/572/004 – 12 tablets
EU/1/09/572/005 – 40 tablets

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

16 October 2009

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicine is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

VANTAVO 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 D_3).

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

VANTAVO is indicated for the treatment of postmenopausal osteoporosis in patients who are not receiving vitamin D supplementation and are at risk of vitamin D insufficiency.
VANTAVO reduces the risk of vertebral and hip fractures.

4.2 Posology and method of administration

Posology

The recommended dose is one VANTAVO tablet once weekly.

Patients should be instructed that if they miss a dose of VANTAVO 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, VANTAVO 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 VANTAVO 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). The equivalence of intake of 5600 IU of vitamin D_3 weekly in VANTAVO to daily dosing of vitamin D 800 IU has not been studied.

Elderly population:
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:
VANTAVO is not recommended for patients with renal impairment where GFR is less than 35 ml/min, due to lack of experience. No dose adjustment is necessary for patients with a glomerular filtration rate (GFR) greater than 35 ml/min.

Paediatric population:
The safety and efficacy of VANTAVO in children less than 18 years of age has not been established. VANTAVO should not be used in children less than 18 years of age because no data are available.

Method of administration

Oral use.

To permit adequate absorption of alendronate:

VANTAVO 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):

- VANTAVO 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 VANTAVO 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.
- Patients should not lie down for at least 30 minutes after taking VANTAVO.
- VANTAVO 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.
- 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, 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.

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.

Renal insufficiency
VANTAVO is not recommended for patients with renal impairment where GFR 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 VANTAVO (see section 4.3). Other disorders affecting mineral metabolism (such as vitamin D deficiency and hypoparathyroidism) should also be effectively treated before starting VANTAVO. The content of vitamin D in VANTAVO 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 VANTAVO.

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, 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).

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

VANTAVO 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 adequate data from the use of VANTAVO 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).

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

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 fetal risk in humans. However, there is a theoretical risk of fetal harm, predominantly skeletal, if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on the risk has not been studied.

4.7 Effects on ability to drive and use machines

Certain adverse reactions that have been reported with VANTAVO may affect some patients' ability to drive or operate machinery. Individual responses to VANTAVO may vary (see section 4.8).

4.8 Undesirable effects

The most commonly reported adverse reactions are upper gastrointestinal adverse reactions including abdominal pain, dyspepsia, oesophageal ulcer, dysphagia, abdominal distension and acid regurgitation ($\geq 1/100$ to $< 1/10$).

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 VANTAVO.

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)

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[†]
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 photosensitivit y, severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis[‡]
Musculoskeletal and connective tissue disorders:	*Very common:* musculoskeletal (bone, muscle or joint) pain which is sometimes severe[†§] *Common:* joint swelling[†] *Rare:* osteonecrosis of the jaw[‡§]; atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction)[⊥]
General disorders and administration site conditions:	*Common:* asthenia[†], peripheral oedema[†] *Uncommon:* transient symptoms as in an acute-phase response (myalgia, malaise and rarely, fever), typically in association with initiation of treatment[†]

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

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 VANTAVO, 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

VANTAVO is a combination tablet containing the two active substances alendronate sodium trihydrate and colecalciferol (vitamin D_3).

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-mobilizing 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.

VANTAVO studies
The effect of the lower dose of VANTAVO (alendronate 70 mg/vitamin D_3 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 VANTAVO (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 VANTAVO (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 VANTAVO (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 VANTAVO (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 VANTAVO (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 VANTAVO (alendronate 70 mg/vitamin D_3 2800 IU) plus an additional 2800 IU Vitamin D_3 for a total of 5600 IU (the amount of vitamin D_3 in the higher dose of VANTAVO) once weekly was demonstrated in a 24-week, extension study that enrolled 619 osteoporotic post-menopausal women. Patients in the Vitamin D_3 2800 group received VANTAVO (70 mg/2800 IU) (n=299) and patients in the Vitamin D_3 5600 group received VANTAVO (70 mg/2800 IU) plus an additional 2800 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 5600 group (69 nmol/l [27.6 ng/ml]) than in the Vitamin D_3 2800 group (64 nmol/l [25.5 ng/ml]). The percentage of patients with vitamin D insufficiency was 5.4 % in the Vitamin D_3 2800 group vs. 3.2 % in the Vitamin D_3 5600 group through the 24-week extension. The percentage of patients with vitamin D deficiency was 0.3 % in the Vitamin D_3 2800 group vs. zero in the Vitamin D_3 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 %).

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

similar in both treatment groups.

5.2. Pharmacokinetic properties

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 VANTAVO (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 [^{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 VANTAVO 70 mg/5600 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 5600 IU vitamin D_3 in VANTAVO is similar to 5600 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 VANTAVO (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
Silica, colloidal anhydrous
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/1/09/572/006 – 2 tablets
EU/1/09/572/007 – 4 tablets
EU/1/09/572/008 – 12 tablets
EU/1/09/572/009 – 40 tablets

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

16 October 2009

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicine is available on the website of the European Medicines Agency http://www.ema.europa.eu

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

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

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, presented in Module 1.8.1 of the Marketing Authorisation, 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 04 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.

The MAH should submit an updated Risk Management Plan reflecting "atypical femoral fractures" as potential risk. The Risk Management plan should be submitted by 6 October 2011.

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 European Medicines Agency

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

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

VANTAVO 70 mg/2800 IU tablets
Alendronic acid /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 D_3).

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
6 tablets
12 tablets
40 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

To be taken once weekly, on the same day each week. Read the package leaflet before use.
For oral 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/1/09/572/001 (2 tablets)
EU/1/09/572/002 (4 tablets)
EU/1/09/572/003 (6 tablets)
EU/1/09/572/004 (12 tablets)
EU/1/09/572/005 (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

VANTAVO
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

VANTAVO 70 mg/2800 IU tablets
Alendronic acid /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 D_3).

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 VANTAVO 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 **VANTAVO** 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 **VANTAVO once** each week on that same day for as long as your doctor prescribes it.

If you miss a dose, take only one **VANTAVO** 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 **VANTAVO** 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 **VANTAVO**.

VANTAVO
WEEK 1
VANTAVO
WEEK 2
VANTAVO
WEEK 3
VANTAVO
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
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United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/572/001 (2 tablets)
EU/1/09/572/002 (4 tablets)
EU/1/09/572/003 (6 tablets)
EU/1/09/572/004 (12 tablets)
EU/1/09/572/005 (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

VANTAVO 70 mg/5600 IU tablets
Alendronic acid /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 D_3).

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

To be taken once weekly, on the same day each week. Read the package leaflet before use.
For oral 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/1/09/572/006 (2 tablets)
EU/1/09/572/007 (4 tablets)
EU/1/09/572/008 (12 tablets)
EU/1/09/572/009 (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

VANTAVO
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

VANTAVO 70 mg/5600 IU tablets
Alendronic acid /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 D_3).

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 VANTAVO 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 **VANTAVO** 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 **VANTAVO once** each week on that same day for as long as your doctor prescribes it.

If you miss a dose, take only one **VANTAVO** 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 **VANTAVO** 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 **VANTAVO**.

VANTAVO
WEEK 1
VANTAVO
WEEK 2
VANTAVO
WEEK 3
VANTAVO
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

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12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/572/006 (2 tablets)
EU/1/09/572/007 (4 tablets)
EU/1/09/572/008 (12 tablets)
EU/1/09/572/009 (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

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

VANTAVO 70 mg/2800 IU tablets
Alendronic acid /colecalciferol

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 VANTAVO, before taking this medicine.

In this leaflet:

1. What VANTAVO is and what it is used for
2. Before you take VANTAVO
3. How to take VANTAVO
4. Possible side effects
5 How to store VANTAVO
6. Further information

1. WHAT VANTAVO IS AND WHAT IT IS USED FOR

What is VANTAVO?
VANTAVO is a tablet containing the two active substances, alendronic acid 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 VANTAVO used for?
Your doctor has prescribed VANTAVO to treat your osteoporosis and because you are at risk of vitamin D insufficiency. VANTAVO reduces the risk of spine and hip fractures in women after menopause.

VANTAVO 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. VANTAVO 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 VANTAVO, 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 VANTAVO

Do not take VANTAVO
- 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 VANTAVO
It is important to tell your doctor before taking VANTAVO if:
- you suffer from kidney problems,
- you have 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 low blood calcium,
- 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 corticosteroids (such as prednisone or dexamethasone),
- 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 VANTAVO.

It is important to maintain good oral hygiene when being treated with VANTAVO. 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 VANTAVO. These side effects may worsen if patients continue to take VANTAVO after developing these symptoms.

Use in children
VANTAVO should not be given to children less than 18 years of age.

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

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

It is likely that certain medicines or food additives may prevent the vitamin D in VANTAVO 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.

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

Pregnancy and breast-feeding
VANTAVO is only intended for use in postmenopausal women. You should not take VANTAVO 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 VANTAVO that may affect your ability to drive or operate machinery. (See POSSIBLE SIDE EFFECTS.) If you experience any of these side effects you should not drive until you feel better.

Important information about some of the ingredients of VANTAVO
VANTAVO 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 VANTAVO

Always take VANTAVO exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Take one VANTAVO tablet <u>once a week</u>.

Follow these instructions carefully to make sure you will benefit from VANTAVO.

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

It is very important to follow instructions 2), 3), 4) and 5) to help the VANTAVO 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 VANTAVO 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 VANTAVO 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 VANTAVO and contact your doctor.

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

If you take more VANTAVO 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 VANTAVO
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 VANTAVO
It is important that you continue taking VANTAVO for as long as your doctor prescribes the medicine. VANTAVO can treat your osteoporosis only if you continue to take the tablets.

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, VANTAVO can cause side effects, although not everybody gets them.
The frequency of possible side effects listed below is defined using the following convention:
very common (affects more than 1 user in 10)
common (affects 1 to 10 users in 100)
uncommon (affects 1 to 10 users in 1,000)
rare (affects 1 to 10 users in 10,000)
very rare (affects less than 1 user in 10,000)

Very common:
- bone, muscle and/or joint pain which is sometimes severe.

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,
- 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:
- 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:
- 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),
- rash made worse by sunlight; 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,
- mouth ulcers when the tablets have been chewed or sucked.

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

5. HOW TO STORE VANTAVO

Keep out of the reach and sight of children.

Do not use VANTAVO 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 VANTAVO contains

The active substances are alendronic acid and colecalciferol (vitamin D_3). Each tablet contains 70 mg alendronic acid as alendronate sodium trihydrate and 70 micrograms (2800 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), butyl hydroxytoluene (E321), modified starch (maize), and sodium aluminium silicate (E554).

What VANTAVO looks like and contents of the pack

VANTAVO 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
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Hertford Road, Hoddesdon
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United Kingdom

Manufacturer
Merck Sharp & Dohme BV
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2031 BN, Haarlem, Netherlands

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

Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu

PACKAGE LEAFLET: INFORMATION FOR THE USER

VANTAVO 70 mg/5600 IU tablets
Alendronic acid /colecalciferol

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 VANTAVO, before taking this medicine.

In this leaflet:

1. What VANTAVO is and what it is used for
2. Before you take VANTAVO
3. How to take VANTAVO
4. Possible side effects
5. How to store VANTAVO
6. Further information

1. WHAT VANTAVO IS AND WHAT IT IS USED FOR

What is VANTAVO?
VANTAVO is a tablet containing the two active substances, alendronic acid 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 VANTAVO used for?
Your doctor has prescribed VANTAVO to treat your osteoporosis and because you are at risk of vitamin D insufficiency. VANTAVO reduces the risk of spine and hip fractures in women after menopause.

VANTAVO 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. VANTAVO 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 VANTAVO, 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 VANTAVO

Do not take VANTAVO
- 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 VANTAVO
It is important to tell your doctor before taking VANTAVO if:
- you suffer from kidney problems,
- you have 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 low blood calcium,
- 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 corticosteroids (such as prednisone or dexamethasone),
- 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 VANTAVO.

It is important to maintain good oral hygiene when being treated with VANTAVO. 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 VANTAVO. These side effects may worsen if patients continue to take VANTAVO after developing these symptoms.

Use in children
VANTAVO should not be given to children less than 18 years of age.

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

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

It is likely that certain medicines or food additives may prevent the vitamin D in VANTAVO 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.

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

Pregnancy and breast-feeding
VANTAVO is only intended for use in postmenopausal women. You should not take VANTAVO 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 VANTAVO that may affect your ability to drive or operate machinery. (See POSSIBLE SIDE EFFECTS.) If you experience any of these side effects you should not drive until you feel better.

Important information about some of the ingredients of VANTAVO
VANTAVO 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 VANTAVO

Always take VANTAVO exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Take one VANTAVO tablet <u>once a week</u>.

Follow these instructions carefully to make sure you will benefit from VANTAVO.

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

It is very important to follow instructions 2), 3), 4) and 5) to help the VANTAVO 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 VANTAVO 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 VANTAVO 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 VANTAVO and contact your doctor.

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

If you take more VANTAVO 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 VANTAVO
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 VANTAVO
It is important that you continue taking VANTAVO for as long as your doctor prescribes the medicine. VANTAVO can treat your osteoporosis only if you continue to take the tablets.

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

4. POSSIBLE SIDE EFFECTS

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

The frequency of possible side effects listed below is defined using the following convention:
very common (affects more than 1 user in 10)
common (affects 1 to 10 users in 100)
uncommon (affects 1 to 10 users in 1,000)
rare (affects 1 to 10 users in 10,000)
very rare (affects less than 1 user in 10,000)

Very common:
- bone, muscle and/or joint pain which is sometimes severe.

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,
- 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:
- 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:
- 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),
- rash made worse by sunlight; 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 osteroporosis 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,
- mouth ulcers when the tablets have been chewed or sucked.

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

5. HOW TO STORE VANTAVO

Keep out of the reach and sight of children.

Do not use VANTAVO 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 VANTAVO contains

The active substances are alendronic acid 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 VANTAVO looks like and contents of the pack

VANTAVO 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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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

Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu

ANNEX IV

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS OR FOR PRESENTED BY THE EUROPEAN MEDICINES AGENCY

Scientific conclusions

Overall summary of the scientific evaluation of Vantavo

Bisphosphonates are medicinal products that are used to treat and prevent bone disorders including hypercalcaemia and the prevention of bone problems in patients with cancer, the treatment of osteoporosis and Paget's disease.

Following a Pharmacovigilance Working Party (PhVWP) review in 2008, it was concluded that a warning about atypical stress fractures of the proximal femoral shaft would be added to the product information for alendronic acid containing medicinal products across Europe. This issue was considered again by the PhVWP in April 2010, as cases had been reported in association with other bisphosphonates, supporting the view that atypical stress fractures are a class effect of bisphosphonates.

Further to the PhVWP discussions and the emerging data from both the published literature and post-marketing reports that suggest that atypical stress fractures may be a class effect of bisphosphonates, the, the European Commission initiated a procedure under Art 20 of Regulation (EC) No 726/2004 for bisphosphonate-containing products and referred the matter to the CHMP, to give its opinion on measures necessary to ensure the safe and effective use of these medicinal products and whether the Marketing Authorisations should be maintained, varied, suspended or withdrawn.

The CHMP reviewed the available data from non-clinical and histological studies, relevant clinical trials, epidemiological studies, post-marketing reports and published literature.

Non-clinical data

Although pre-clinical studies have provided limited information on the risk of atypical fractures with bisphosphonates, some of them have demonstrated that suppression of bone turnover by bisphosphonates may increase microdamage accumulation and the accumulation of advanced glycation end-products resulting in changes in the biomechanical properties of bone (Brennan et al, 2011, Hofstaetter et al, 2010, Mashiba et al, 2000, O'Neal et al, Tang et al, 2009[1]). However not all pre-clinical studies have found adverse effects of alendronic acid on bone (Burr et al[2]).

Definition of atypical fracture of the femur

The task force of the American Society for Bone and Mineral Research (ASBMR) on atypical subtrochanteric and diaphyseal femoral fractures have defined major and minor features of atypical femoral fracture (Shane et al, 2010[3]) and recommend that for a case to be considered an atypical femoral fracture all major features need to be present, whereas the minor features have commonly been described in cases of atypical femoral fractures, but are not present in all patients.

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[1]Brennan O et al The effects of estrogen deficiency and bisphosphonate treatment on tissue mineralisation and stiffness in an ovine model of osteoporosis. J Biomech 2011; 44:386-90
Hofstaetter JG et al. The effects of high-dose, long-term alendronate treatment on microarchitecture and bone mineral density of compact and trabecular bone in the proximal femur of adult male rabbits. Arch Orthop Trauma Surg 2010; 30: 937-944
Mashiba T et al Suppressed bone turnover by bisphosphonates increases microdamage accumulation and reduces some biomechanical properties in dog rib. J Bone Miner Res 2000; 15: 613-620
O'Neal JM et al One year of alendronate treatment lowers microstructural stresses associated with trabeclar microdamage initiation. Bone 2010; 47: 241-247
Tang SY et al Changes in non-enzymatic glycation and its association with altered mechanical properties following 1-year treatment with risedronate or alendronate. Osteoporosis Int 2009; 20: 887-894

[2] Burr DB et al Effects of one to three years treatment with alendronate on mechanical properties of the femoral shaft in a canine model: implications for subtrochanteric femoral fracture risk. J Orthop Res 2009; 27: 1288-1292

[3] Shane E et al Atypical subtrochanteric and diaphyseal femoral fractures: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res 2010; 25: 2267-2294

Based on the small number of spontaneous reports of comminuted atypical femoral fracture in association with bisphosphonates, one published case report (Schneider, 2006[4]), as well as preliminary data presented at the October meeting of the ASBMR (Nitche et al, 2010[5]), the CHMP for the purpose of its assessment agreed on a modified case definition that lists 'noncomminuted' as a minor feature rather than a major feature of atypical femur femoral fracture.

Mechanism of atypical fractures

The mechanism(s) for the development of atypical fractures in patients taking bisphosphonates is not known. However a number of possible mechanisms of atypical fracture in association with bisphosphonate use have been postulated. The main postulated mechanism is the suppression of bone turnover leading indirectly to ageing bone and the delay or prevention of repair of naturally occurring stress fractures although the evidence is not conclusive.

Epidemiological studies

While some epidemiology studies suggest that subtrochanteric and femoral shaft fractures may be normal osteoporotic fractures (Abrahamsen et al, 2009[6], Abrahamsen, 2010[7], Vestergaard et al, 2010[8]) other studies suggest that long-term bisphosphonate use may increase the risk of subtrochanteric and femoral shaft fractures (Park-Wyllie et al, 2011[9], Wang & Bhattacharyya, 2011[10]). However these studies do not specifically relate to atypical fracture of the femur as they do not contain information about radiographic fracture pattern.

Evidence from studies that do provide specific information about atypical femoral fractures identified from radiographs suggests that these fractures may be causally related to bisphosphonate use. Case-control studies have reported a significant association between atypical femur fracture pattern and bisphosphonate use (Lenart et al, 2009[11], Isaacs et al, 2010[12]). Other studies with radiographic evidence have also reported an increased incidence of atypical femoral fractures in patients treated with bisphosphonates compared to non-exposed patients, which may increase with duration of bisphosphonate treatment (Dell et al, 2010[13], Schilcher et al, 2009[14]).

Post-marketing reports

The number of post-marketing reports of possible atypical femur fracture suspected to be associated with bisphosphonates has increased since the 2008 PhVWP review. Although the highest number of possible atypical femoral fracture continue to be reported in association with alendronic acid for

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[4] Schneider P. Should bisphosphonates be continued indefinitely? An unusual fracture in a healthy woman on long-term alendronate. Geriatrics 2006; 61: 31-33

[5] Nitche J et al Subtrochanteric femoral stress fractures in patients on chronic bisphosphonate therapy: a case series. J Bone Miner Res 25 (Suppl 1) 2010; Available at http://www.asbmr.org/Meetings/AnnualMeeting/AbstractDetail.aspx?aid=223582c5-f5bb-4d66-bd16-d073267b2a47. Accessed 5 April 2011

[6] Abrahamsen B et al Subtrochanteric and diaphyseal femur fractures in patients treated with alendronate: a register-based national cohort study. J Bone Miner Res 2009; 24: 1095-1102

[7] Abrahamsen B et al Cumulative alendronate dose and the long term absolute risk of subtrochanteric and diaphyseal femur fractures: a register-based national cohort analysis. J Clin Endocrinol Metab 2010; 95:5258-5265

[8] Vestergaard P et al Risk of femoral shaft and subtrochanteric fractures among users of bisphosphonates and raloxifene. Osteoporos Int 2010; DOI 10.1007/s00198-010-1512y

[9] Park-Wyllie LY et al Bisphosphonate Use and the Risk of Subtrochanteric or Femoral Shaft Fractures in Older Women. JAMA 2011; 305:783-789

[10] Wang Z & Bhattacharyya T Trends in Incidence of Subtrochanteric Fragility Fractures and Bisphosphonate Use Among the US Elderly, 1996–2007. J Bone Miner Res 2011; DOI 10.1002/jbmr.233

[11] Lenart BA et al Association of low-energy femoral fractures with prolonged bisphosphonate use: a case control study. Osteoporos Int 2009; 20: 1353-1362

[12] Isaacs JD et al Femoral insufficiency fractures associated with prolonged bisphosphonate therapy. Clin Orthop Relat Res 2010; 468: 3384-3392

[13] Dell R et al A retrospective analysis of all atypical femur fractures seen in a large California HMO from the years 2007 to 2009. J Bone Miner Res 25 (Suppl 1) 2010; Available at http://www.asbmr.org/Meetings/AnnualMeeting/AbstractDetail.aspx?aid=05caf316-b73e-47b8-a011-bf0766b062c0. Accessed 15 February 2011

[14] Schilcher J et al Incidence of stress fractures of the femoral shaft in women treated with bisphosphonates. Acta Orthopaedica 2009; 80: 413-415

osteoporosis, post-marketing reports have also been reported for other bisphosphonates for osteoporosis (etidronic acid, ibandronic acid, risedronic acid and zoledronate), and also for Paget's disease (zoledronate) and oncology indications (ibandronic acid, pamidronic acid and zoledronate), suggesting that these fractures may be a class effect of bisphosphonates. The lack of reports with the remaining bisphosphonates, clodronic acid, neridronic acid and tiludronic acid may be related to the lower exposure of these medicinal products compared with other bisphosphonates and a lack of an association can not be excluded.

At the present time there is little evidence from literature and spontaneous reports to support an association between bisphosphonates and atypical fracture at sites other than the femur. The lack of evidence may be due to a lack of recognition and reporting of atypical fractures at sites other than the femur with bisphosphonate use or it is possible that the unique characteristics of the femur as the major weight bearing bone in the body mean that atypical fractures only occur at this site. The potential risk of atypical fractures at sites other than the femur will be kept under review.

Risk factors

A number of possible risk factors have been proposed for atypical femoral fractures in association with bisphosphonate use. The long-term use of bisphosphonates is thought to be the main risk factor for atypical femoral fractures. However, the optimal duration of use of bisphosphonates for osteoporosis is not known. There is currently no robust evidence regarding the value of interrupting treatment with bisphosphonates. Glucocorticoids and proton pumps inhibitor (PPI) have been identified as possible important risk factors for atypical femur fracture. Concomitant treatment with other anti-resorptive drugs such as hormone replacement therapy and raloxifene have also been proposed as possible risk factors. Other than osteoporosis the most prevalent co-morbid conditions in patients with atypical femur fracture were found to be chronic obstructive pulmonary disease or asthma, rheumatoid arthritis and diabetes.

Overall conclusion

Taking into account all the available evidence, the CHMP concluded that use of biphosphonates can be associated with the risk of atypical femoral fractures and therefore recommended that the following information is included in the Product Information of all biphosphonates:

- Addition of a warning in section 4.4 of the SmPC (Special warnings and precautions for use) to reflect this risk , the main features of these fractures and the potential need for discontinuation of treatment in case a fracture is suspected.
- Addition of atypical femoral fracture to section 4.8 (Undesirable effects) of the SmPC accompanied by a statement that this adverse effect is a class attribution of all bisphosphonates.

In addition, given the lack of evidence regarding the optimal duration of bisphosphonate treatment for osteoporosis, and considering that duration of treatment is a risk factor for atypical femoral fractures, the CHMP also recommended that information should be added to section 4.2. of the product information for bisphosphonates authorised for osteoporosis, about the need to periodically evaluate the need for continuing bisphosphonate treatment, particularly after 5 years of treatment, on an individual patient basis.

The CHMP concluded that the findings of this review do not change the overall balance of risks and benefits of individual bisphosphonates in their authorised indications.

Grounds for amendment of the summary of product characteristics and package leaflet

Whereas

- The Committee considered the procedure under Article 20 of Regulation (EC) No 726/2004, for Vantavo initiated by the European Commission.

- The Committee considered all the available data submitted (pre-clinical, clinical, epidemiological studies, post-marketing reports, published literature) in relation to the risk of atypical femoral fractures with biphosphonates.

- On the basis of the available evidence, mainly from epidemiological studies and post-marketing reports, the Committee concluded that use of bisphosphonates may be associated with the risk of atypical femoral fractures. The CHMP also concluded that main risk factor associated with these fractures appears to be long-term bisphosphonate treatment.

- The Committee concluded that the Product Information of all bisphopshonates should include a warning in section 4.4 on the risk of atypical fractures of the femur and this adverse reaction should also be listed in section 4.8 of the SPCs. The Committee also concluded that information should be added to section 4.2. of the product information for bisphosphonates authorised for osteoporosis, about the need to periodically evaluate the need for continuing bisphosphonate treatment, particularly after 5 years of treatment, on an individual patient basis.

In view of the above, the CHMP has recommended the variation of the Marketing Authorisations for Vantavo (see Annex A), for which the Summary of Product Characteristics and Package Leaflet are set out in Annex I and III B and subject to the conditions set out in Annex II of this Opinion.