SCIENTIFIC DISCUSSION

1. Introduction

FOSAVANCE is presented as a fixed combination tablet containing 70 mg alendronic acid (as alendronate sodium trihydrate) and 70 micrograms (2800 IU) colecalciferol (vitamin D_3). It is intended as a once weekly treatment of postmenopause osteoporosis.

Postmenopausal osteoporosis is characterised by a reduction in bone mass and strength resulting from a compromise of bone density and/or bone architecture, leading to increased fragility and fracture risk. The main reason for this process is that oestrogen deficiency after the menopause results in an imbalance between bone resorption and bone formation, favouring the former. Osteoporosis is defined as bone mineral density (BMD) expressed as T-scores, i.e. the number of standard deviations (SD) difference from the mean value of healthy premenopause women in the spine and/or hip, of -2.5 or lower. It is estimated that 40% of women aged 50, or over, will develop an osteoporosis-related fracture during their remaining lifetime and the incidence in Europe, over 1 million cases per annum, is associated with significant morbidity, mortality and economic burden.

The ultimate goal of pharmacological treatment of women with postmenopause osteoporosis is to reduce the risk of fractures by increasing bone mass of normal quality. There are several compounds currently authorised for the treatment and/or prevention of postmenopausal osteoporosis including bisphosphonates, selective oestrogen-receptor modulators, as well as estrogens (now second-line therapy, because of safety concerns regarding hormonal replacement therapy).

Alendronate is a nitrogen-containing bisphosphonate which selectively inhibits osteoclast-mediated bone resorption. It has been shown to inhibit and partially reverse the progression of osteoporosis, resulting in increased BMD with histologically normal bone and decreased fracture incidence. A medicinal product containing alendronate has already been authorised throughout the EU for postmenopause osteoporosis as a 10 mg daily dose and more recently as a 70 mg weekly dose.
Vitamin D_3 is an essential for calcium absorption and therefore for normal bone formation. The main source is from sunlight exposure. Vitamin D insufficiency develops when both sunlight exposure and dietary intake are inadequate.

The rationale for the proposed alendronate/colecalciferol combination product is that it would ensure, in a simple one tablet a week regimen, a level of vitamin D supplementation which would help to provide a background of adequate vitamin D status upon which alendronate can act.

The approved indication is: “Treatment of postmenopausal osteoporosis in patients at risk of vitamin D insufficiency. FOSAVANCE reduces the risk of vertebral and hip fractures”.

2. Quality aspects

FOSAVANCE is presented as tablets containing 70 mg alendronic acid (as alendronate sodium trihydrate) and 70 micrograms (2800 IU) colecalciferol (vitamin D_3) as active substances.

Excipients include microcrystalline cellulose, lactose anhydrous, medium chain triglycerides, gelatin, croscarmellose sodium, sucrose, colloidal silicon dioxide, magnesium stearate, butylated hydroxytoluene, modified food starch and sodium aluminum silicate.

Tablets are supplied in push-through all aluminium blisters.

Active Substances

Alendronate sodium

This active substance is a white or almost white, crystalline powder, and is the subject of a monograph in the Ph Eur. The aqueous solubility of alendronate sodium is 40.0 mg/ml; it is practically insoluble in organic solvents. Alendronate sodium has been demonstrated to be not hygroscopic. The drug substance is achiral, not optically active, and there is no evidence of polymorphism. The chemical name is (4-Amino-1-hydroxybutylidene) bisphosphonic acid monosodium salt trihydrate.

Alendronate sodium is synthesised in a two-step process. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents, have been presented. The three-production scale batch data presented show a reproducible manufacturing process leading to homogeneous batches.

This active substance is tested according to the specifications established in the Ph Eur. Monograph. The active substance specification includes tests for appearance, identity of the active substance (IR), identity of sodium, assay (HPLC, 99.0-101.0 % w/w), impurities (HPLC), heavy metals, lost of drying, degree of coloration, opalescence, pH, phosphates / phosphates and particle size.

The specifications reflect all relevant quality attributes of the active substance. The analytical methods used in the routine controls are suitability described. The validation studies are in accordance with the ICH Guidelines.

Alendronate sodium has been stored at the ICH conditions of 25ºC/60%RH and 40ºC/75%RH in double polyethylene bags in fiberboard containers. Stability tests included assay and impurities by HPLC and testing on loss on drying. Additionally, alendronate sodium has been exposed to extreme thermal, humidity, photolytic, acidic, basic and oxidative stress conditions to induce the formation of potential degradation products and to demonstrate the stability indicating nature of the applied HPLC analytical procedures. All results submitted comply with the proposed specification, it was demonstrated to be a very stable substance. Therefore, the re-test period proposed is acceptable according to the stability data submitted.

Colecalciferol (vitamin D3)

Colecalciferol is practically insoluble in water (it is a fat-soluble vitamin) and it is sensitive to air, heat and light. Therefore, it is presented as colecalciferol concentrate (powder form) Ph Eur, which is a formulated material to improve the stability of the active substance.
Colecalciferol concentrate, powder form is a formulation of colecalciferol dissolved in medium chain triglycerides, embedded in a modified food starch coated matrix based on a combination of gelatin and sucrose to form granules. The product contains butylated hydroxytoluene (BHT) as an antioxidant and sodium aluminum silicate as an anti-caking agent. Given this, the bioavailability of colecalciferol will be dependant upon the disintegration of the tablet.

Information on colecalciferol has been supplied in the form of an ASMF (Active Substance Master File).

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents, have been presented.

Colecalciferol concentrate (powder form) specification includes tests for characteristics, identity (HPLC, Ph Eur, NIR), assay (HPLC), impurities (HPLC), assay BHT (HPLC), Lost on drying (Ph Eur), particle size (Ph Eur) and microbial limits.

Two stability studies were provided to support the proposed retest period: (1) a twelve-month primary stability study for four commercial batches. All batches stored in laminated aluminium-foil bags were tested according to ICH-conditions. Humidity is not controlled and this was justified by data showing

that the proposed laminate packing is impermeable to moisture. No significant changes were observed. The data support extrapolation and justify the proposed retest period (2) 36 month supportive stability for three production scale batches, packed in the proposed packing, the storage temperatures were 25˚C and 40˚C.
The re-test period proposed was considered acceptable according to the stability data submitted.

Medicinal Product

- Pharmaceutical Development

The intention was to develop a physical and chemical stable dosage form, which provides a once-weekly dose of both alendronate sodium and colecalciferol.
Due to the instability of colecalciferol, the development was focused on a suitable, commercially available, stabilised vitamin D_3 granulation formulation. Finally, colecalciferol concentrate, powder form was chosen as a commercial formulation. The particle size of the granule is satisfactorily controlled in the Active Substance Specification.
The development pharmaceutics is comprehensive and the proposed formulation and the standard method of manufacture was satisfactorily justified.
The batches used in the clinical studies are the same quality as that proposed for marketing.

The excipients chosen for the proposed commercial product are the same as those that were selected during early development. Selection of the excipients was based on the goal of developing a physical and chemical stable formulation. Most of the excipients chosen are the same as those currently used in the Alendronate Sodium Tablet formulation. Colloidal silicon dioxide was added to the combination tablet formulation to improve the flow of the lubricated powder blend, vegetable-based magnesium stearate is used.
All excipients are of Ph. Eur. quality and commonly used within pharmaceutical solid dosage forms.

The finished product contains the excipients lactose anhydrous and magnesium stearate, which are the only ingredients that may be of ruminant origin. Lactose anhydrous is derived from milk that satisfies the requirements outlined in the TSE Guideline (EMEA/410/01 rev 2). Magnesium stearate is derived from purely vegetable source.

The active material colecalciferol concentrate (powder form) contains one ingredient of ruminant origin, wool grease from which the vitamin D3 is synthetically derived, for which a satisfactory TSE certificate of suitability has been provided. Colecalciferol concentrate (powder form) also contains gelatin, for which satisfactory confirmation is provided that it is of porcine, not ruminant, origin.

As primary packaging materials push-through all aluminium blisters are used. The identity of plastic materials is controlled routinely.

- Manufacture of the Product

Product manufacture consists of standard processes including mixing, blending, dry granulation and compression.

The release testing batch results presented show sufficient quality of the product, this can be regarded acceptable. A summary protocol for the validation study was provided.
In process controls are adequate for this tablet preparation.
The 3 commercial batch analysis data provided show that the tablets can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of this oral preparation.

- Product Specification

The product specifications include tests by validated methods for appearance, assay of the active substances (95-105%, HPLC), identity of the active substances (HPLC, TLC), degradates (HPLC), content uniformity (HPLC), dissolution (HPLC), moisture (Karl Fischer or NIR) and microbial limit

(Ph Eur). Degradation products are controlled and their limits are justified by reference to stability studies and toxicology studies.
Tests and limits of the specifications for the finished product are appropriate to control the quality of the finished product for their intended purpose.

Batch analysis data on four pilot-scale batches confirm satisfactory uniformity of the product at release.

- Stability of the Product

The primary stability data consisted of three pilot batches packed in a number of primary containers, including those proposed for marketing.

The storage conditions comply with ICH requirements, consisting of 25°C/60%RH, 30°C/65%RH and 40°C/75%RH. Up to 51 weeks stability data are provided.

Stability investigation were performed according to the methods of Finished Product Specification and included tests for appearance, sodium alendronate and vitamin D_3 assay, vitamin D_3 degradation products, sodium alendronate dissolution, and moisture, except that the sodium alendronate assay was a slightly different HPLC assay procedure for which satisfactory methodology and validation are provided.

Tests in addition to those specified in the Finished Product Specification include vitamin D_3 dissolution, BHT assay, sodium alendronate degradation product 2-phosphonopyrrolidine, hardness, disintegration and microbial limit testing. Appropriate methodology and validation data have been provided.

Three month stability data at long term 25°C/60%RH and accelerate conditions 40°C/75%RH ICH conditions for three production batches are also provided.

Based on available stability data, the proposed shelf life and storage conditions as stated in the Summary of Product Characteristics are acceptable.

Bioequivalence

Two pilot studies were conducted prior to the definitive bioequivalence study to ensure there was no evidence that co-administration affected alendronate bioavailability, to gain experience with a new mass spectrometry vitamin D_3 assay, and to obtain preliminary variability estimates.

A main study was conducted to demonstrate that there was no pharmacokinetic interaction between alendronate sodium and colecalciferol when taken in the proposed marketed product. The study consisted of two parts: (1) an open-label, randomised, two period, crossover single centre bioequivalence study to determine the relative bioavailability of alendronate from FOSAVANCE compared to alendronate tablet medicinal product and (2) an open-label, randomised, two period, crossover single centre bioequivalence study to determine the relative bioavailability of colecalciferol from FOSAVANCE compared to a specially manufactured vitamin D_3 2800IU tablet.

The data adequately demonstrated that there is no significant pharmacokinetic interaction between the two active substances in the proposed combination product.

These studies are further presented under the part 3.4 Clinical aspects in the section related to pharmacokinetics data.

3. Non-clinical aspects

Introduction

The applicant had previously conducted a comprehensive programme to investigated the pharmacology, pharmacokinetics and toxicology of alendronate alone. For vitamin D_3, given that it is a natural metabolite of cholesterol upon sunlight exposure and is used as nutritional supplementation, no studies were conducted but an extensive review of the literature of non-clinical studies of vitamin D_3 or its metabolites was provided. The toxicology data on vitamin D_3 are mainly based on studies with calcitriol, a synthetic hormonal metabolite of vitamin D_3 , available from the NDA Report 21-068 and NDA Report 18-044/S025 (FDA, 2003, Approval package for Rocaltrol) [1].

No additional studies were conducted with the combination of alendronate with vitamin D_3. It was considered that the extensive literature for vitamin D_3, the comprehensive preclinical data for alendronate, and the clinical experience with co-administration of alendronate and vitamine D_3, superseded the need for additional animal data.

The applicant has provided an overview of the comprehensive information on each active substance. Previous findings with the individual components in relation to pharmacology, pharmacokinetics and toxicology are summarised in the below sections. For vitamin D_3, not all the published references, which were part of the application are listed in this document.

Pharmacology

- Primary pharmacodynamics (in vitro/in vivo)

Alendronate

Alendronate is a nitrogen-containing biphosphonate that inhibits osteoclastic bone resorption. It has no direct effect on bone formation. The mode of action postulates incorporation of alendronate present preferentially on the bone resorption surfaces into the cytoplasm of the osteoclast. The activity of osteoclasts is thereby inhibited. After bone resorption stops, bone formation proceeds on the surfaces containing alendronate, which is then incorporated within the matrix where it is no longer pharmacologically active.

The primary pharmacology of alendronate has been investigated in various animal models. Alendronate was administered intermittently, twice weekly (1.8 or 18 μg/kg s.c.), to ovariectomised rats in a 1-year treatment study and every two weeks (0.05 or 0.25 mg/kg i.v.) to ovariectomised baboons in a 2-years prevention study. Alendronate prevented or reversed the bone changes produced in the estrogen deficient animals. The changes such as increased bone turnover, increase in cancellous bone remodeling, decrease BMD and bone loss were similar as observed in humans following ovariectomy or menopause.
In other animal models of human bone diseases, alendronate was shown to inhibit bone resorption regardless of cause.
In the long-term study in dogs (36 months at doses ranging from 0.25 to 1.0 mg.kg/day) alendronate treatment had no deleterious effect on bone quality, bone strength, or bone dynamics.

Vitamin D3

Various animal pharmacodynamic studies show that vitamin D_3 acts as a prohormone that is readily metabolised to 25-OH vitamin D_3 in the liver. It is then hydroxylated by the 1α-hydroxylase at the 1α position in the kidney. This activating step is tightly controlled by circulating levels of parathyroid hormone, calcitonin and 1,α,25 dihydroxyvitamin vitamin D_3 (1α,25$(OH)_2$ vitamin D_3) itself. The action of 1α, 25$(OH)_2$ vitamin D_3 on bone is mediated via the vitamin D receptor (VDR).

Because vitamin D_3 serves as a prohormone with little intrinsic biological activity towards VDR, most animal studies have been performed using the fully active hormone 1,α25$(OH)_2$ vitamin D_3 or 1,α, hydroxyvitamin D_3, which is readily converted to the hormone by 25-hydroxylation in the kidney.
In ovariectomised rats, 1,α,25$(OH)_2$ D_3 increased serum calcium and prevented the ovariectomy-induced lumbar bone loss. [2]
In ovariectomised rats, 0.1-02 µg/kg 1α-OH vitamin D_3 increased BMD in PTX rats infused with human parathyroid hormone (1-34). 1α-OH vitamin D_3 increased BMD more than vitamin D_3 (with high doses up to 0.4 mg/kg) at a given urinary and serum calcium level. [3]
Pharmacological doses of 1,α,25$(OH)_2$ D_3 combined with a biphosphonate (risedronate) resulted in additive effects in prevented ovariectomy-induced bone loss in rats. This suggests that the mechanism of action of either agent is non-redundant. [4]

Published data on pharmacodynamic effects of the 1α,25$(OH)_2$ vitamin D_3 in knockout mice lacking either VDR or the 1-α hydroxylase enzyme confirm the known targets for the active vitamin D_3 metabolites. For the 1α-hydroxylase, but not the VDR, knockout mice, all bone and cartilage phenotypes were rescued through administration of 1α,25$(OH)_2$ vitamin D_3 suggesting that that 1α,25$(OH)_2$ vitamin D_3 is the essential metabolite responsible for most biological effects.

- Secondary pharmacodynamics

No studies were conducted and no additional data were considered necessary.

- Safety pharmacology

Alendronate was studied in a battery of tests and was devoid of any significant activity on the cardiovascular, renal, respiratory, gastrointestinal, and central nervous systems.

Vitamin D_3 is a naturally occurring intermediary metabolite in humans that is the obligate precursor of the hormone calcitriol. Because of the extensive human data available on the use of vitamin D_3 in clinical trials and the intended weekly dose of 2800-IU vitamin D_3, which is in accordance with a daily intake of 400-IU vitamin D_3 recommended in guidelines, additional animal safety data were not considered necessary.

- Pharmacodynamic interactions

Alendronate acts on bone independently of hormonal systems and has no known interaction with vitamin D. The extensive human data available on the concurrent use of alendronate and vitamin D_3 in clinical trials supersedes the need for any additional animal data.

Pharmacokinetics

The pharmacokinetics profile of alendronate had previously been evaluated in mice, rats, dogs and monkeys using validated methods. The pharmacokinetic data of vitamin D_3 derive from the published literature.

Absorption

Alendronate

Alendronate, like all bisphosphonates, is absorbed poorly in animals. Since alendronate is not metabolised and is largely deposited in bone (60 to 70% of i.v. dose), absorption was evaluated by comparing the concentration of alendronate in bone tissues from oral (^{14}C-labeled) and i.v. (^{3}H-labeled) administration. The bioavailability in fasted animals was about 0.2% in the mouse, 0.7% in the rat, 1.8% in the dog, and 1.7% in the monkey. Food markedly decreased the absorption of alendronate in rats. The poor absorption of alendronate (and other bisphosphonates) is most likely attributed to its very poor lipophilicity, which prohibits transcellular transport across the epithelial barriers, and to its relative large molecular size (250 daltons), which hinders paracellular transport.

Vitamin D_3

Vitamin D_3 is absorbed by passive diffusion in the intestine as a fat-soluble vitamin, and requires bile salt for optimal absorption. The normal plasma concentration of vitamin D_3 in animals fed a standard diet (according to the National Research Council) is species dependent, ranging from 0.6ng/ml (sheep) to ca. 10 ng/ml (pig) [5].

Distribution

Alendronate

The plasma protein binding (means ± SD) determined by ultrafiltration at alendronate concentrations of 0.2-10 µg/ml (rat, human) and 0.5-5 µg/ml (dog, monkey) is species-dependent: high to rat plasma proteins (94.76 ± 0.29%), but not to dog (24.6 ± 3.0%), monkey (68.9 ± 3.8%) or human (72.3 ± 3.7 %). At a low concentration range of 0.2 to 0.5 µg/ml, the unbound fraction was about 3% for the rat, 23% for the human, 27% for the monkey and 74% for the dog.

Systemically available alendronate disappears very rapidly from plasma, and it is either taken up by bone tissues or excreted by the kidneys. The uptake of alendronate by bone tissues was species-dependent, likely due to plasma flow rate to bone tissues as well as intrinsic bone uptake, and dose-dependent.

Vitamin D_3

Once absorbed, vitamin D_3 binds to the vitamin D-binding protein in blood [6], which is an α-globulin that serves to transport vitamin D_3 to the liver, where it is stored prior to metabolism to 25-hydroxyvitamin D_3. Vitamin D_3 is well taken up by the liver; the fractional uptake of vitamin D_3 in a single pass across the liver is 40 to 60% in rats and dogs [7].

Metabolism

Alendronate

Alendronate is not metabolised in rats and dogs, a finding reported also for other bisphosphonates.

Vitamin D_3

As already mentioned, vitamin D_3 is inactive and requires sequential hydroxylation in the liver and kidney to become the biologically active form, 1α, 25 dihydroxyvitamin D_3, to exert its role in calcium homeostasis. The enzymes that mediate the hepatic and renal metabolism of vitamin D_3 are the mitochondrial CYP27A1 and CYP27B1, respectively. In rats and pigs, there are microsomal vitamin D_3 25-hydroxylases whose physiological relevance is not well characterised.

The biologically form of vitamin D_3, 1α,25$(OH)_2$ D_3, is metabolically inactivated in a multistep process. The first step is hydroxylation at the 24-position to 1,24,25-trihydroxyvitamin D_3, which is less active [8]. The oxidation of the 24-hydroxy group produces the corresponding ketone, which in turn undergoes oxidative cleavage between C-23 and C-24. This is followed by further oxidation to calcitroic acid, which is inactive. Most, if not all, of these metabolic reactions are mediated by the mitochondrial enzyme, CYP24 (also called P450c24) [8].
An additional elimination pathway for 1α,25$(OH)_2$ D_3 is formation of conjugated metabolites. Following intravenous administration of [^{3}H]1α,25 $(OH)_2$ D_3 to rats, glucuronide, sulfate, taurine, and glycine conjugates were excreted in the bile [9]. The structure of these metabolites has not been definitively determined; however, their chromatographic properties suggest they are likely to be conjugates of calcitroic acid. In addition, 1α, 25$(OH)_2$ D_3 itself is subject to O-glucuronidation without prior oxidation in rats [9].

Excretion

Alendronate

Renal excretion is the only route of elimination of alendronate and urinary recovery is quite similar among species. Following i.v. administration (1 or 0.8 mg/kg) to rats, dogs, and monkeys, approximately 30 to 40% of the dose was excreted in the urine in 24 hours, mostly in the first 3 to 4 hours. Only a very small fraction, less than 0.4% of the dose, was recovered in rat faeces in 24 hours. Detailed studies in rats revealed that alendronate is actively secreted by an uncharacterised renal transport system, but not by anionic or cationic renal transport systems. Because alendronate is not metabolised and has no biliary excretion, compound not excreted in 24 hr post-dose is believed to be sequestered in the skeleton. Once taken up by the bone, the elimination of alendronate from the bone tissue into the circulation to be then eliminated renally is slow, ranging from 200 days in rats to 3 years in dogs.

Vitamin D_3

Following administration of [^{3}H]vitamin D_3 to intact rats, the vast majority of the administered radioactivity (79%) was recovered in faeces, which suggested that vitamin D_3 and its metabolites were eliminated by biliary excretion. Urinary excretion of the vitamin D_3 radioequivalents in rats was quantitatively minor (2.1% of dose) [10].
Following i.v. administration of labeled 1α,25 $(OH)_2$ vitamin D_3 to rats about 24% of the administered radioactivity was excreted in bile within 24 h; only 10% of the excreted radioactivity was unchanged, while 85 to 90% consisted of relatively polar metabolic components. 1α,25 $(OH)_2$ vitamin D_3 t and its metabolites, possibly the glucuronide conjugate, undergo enterohepatic recirculation [11].

Toxicology

- Single dose toxicity

Alendronate
After oral administration, the dose lethal 50 (LD_{50}) in male mice and rats were approximately 1280 and 626 mg/kg, respectively, and in female mice and rats approximately 966 and 552 mg/kg, respectively. The lethality in both species was primarily due to gastrointestinal irritation. The intravenous LD_{50} in male mice and rats were approximately 48 and 42 mg/kg, respectively, and in female mice and rats approximately 51 and 40 mg/kg, respectively. There was no lethality in dogs at single oral doses up to 200 mg/kg, although there was evidence of slight renal toxicity.
Vitamin D_3
After single oral dose of calcitriol or transcalcitriol in neobee oil at 1.0, 2.0, and 4.0 mg/kg in mice, clinical signs of toxicity were only observed in calcitriol-treated animals and included respiratory depression, decreased motor activity, tremors, ptosis, and abnormal gait. At the high-dose all animals died 4 to 9 days post-dose.

- Repeat-dose toxicity

Alendronate

Studies were performed in rats (14 and 53 weeks with oral doses up to 5 mg/kg/day) and in dogs (14 and 27 weeks with oral doses up to 8 mg/kg/day; 53 weeks at 0, 0.5, 2 or 8 mg/kg/day and 8 mg/kg/day for 13 weeks plus a recovery period).

In the rat studies there was no renal, gastrointestinal or liver toxicity observed at oral doses up to 5 mg/kg/day. Toxicity was nonetheless evident with high oral alendronate doses (given up to 150 mg/kg/day) over 14 days in a dose finding carcinogenicity study. In this study renal toxicity (tubular necrosis, increase in serum urea), gastrointestinal toxicity (gastric mucosal degeneration, gastritis,

mucosal erosions or ulcers) and liver toxicity (increases in liver enzymes, ALT, AST) were observed at about 30 mg/kg/day or at higher doses; mortality was observed at doses ≥ 30 mg/kg/day.
In the dog studies, renal toxicity was observed at 4 and 8 mg/kg/day given orally including renal tubular degeneration and chronic focal nephritis, but no marked gastrointestinal effects were observed.

Other effects observed such as reduced serum calcium and serum phosphate, increased urinary excretion of calcium and phosphate in rats and dogs, increase in extramedullary hematopoiesis (rat) are the result of exaggerated pharmacological actions. Retention of primary spongiosa was observed in all repeat dose toxicity studies in rats and dogs and is consistent with a decrease in bone remodelling, a desired pharmacological effect.

The NOAEL in the 53-weeks oral toxicity study in rats was 2.5 mg/kg/day and in the oral 53-weeks dog study 2.0 mg/kg/day.

No toxicokinetics data were obtained for the repeat-dose toxicity studies.

Additional studies were conducted to evaluate the gastric irritation in rats and the oesophageal irritation potential in dogs.
In rats, the potential gastric effects of 3 bisphosphonates (alendronate sodium, risedronate sodium and etidronate sodium) were compared. There were dose-dependent increases in the incidence of gastric lesions involving both the glandular and non-glandular mucosa of the stomach. The no-effect dose levels for gastric lesions were 10, 5, and 200 mg/kg/day orally for alendronate, risedronate and etidronate, respectively.

The studies in anaesthetised dogs were performed with single and repeated intra-esophageal infusion of alendronate over 30 min. Alendronate administered at 0.2 mg/ml (pH=2) in infusion on 5 consecutive days caused esophageal erosions and ulceration. Esophageal infusion twice a week with 0.4 mg/ml alendronate (pH=2) over 4 consecutive weeks resulted in erosive or ulcerative esophagitis, however following infusions with alendronate (50 ml, 0.8 mg/ml, pH=2) once a week for 4 weeks caused no esophageal irritation.

Vitamin D_3

In rats, in a 13-weeks i.v. study (0, 0.05, 0.15 and 0.45 µg/kg/day calcitriol) and a 26-weeks i.v. study (0, 0.05,0.15, 0.45 and 0.9 µg/kg calcitriol, administered intermittently on 3 days/week) signs observed included hypercalcemia, hypercholesterolemia, hypoproteinemia, increased blood urea nitrogen, changes in body weight and organ weights (liver), parathyroid gland atrophy and tissue calcification. There was no treatment-related mortality. The observed changes, such as hypercalcemia, parathyroid gland atrophy, and tissue calcification were considered an exaggerated pharmacological effect of calcitriol. The observed NOAEL was 0.05 µg/kg/day (13-weeks study) and ≤ 0.05 µg/kg/dose (26-weeks study).
In dogs, in a 13-weeks i.v. study (0, 025, 0.05, or 0.1 µg/kg/day calcitriol) the highest dose was discontinued on Day 56 due to excessive mortality. Observed changes were decrease in body weight and food consumption, hypercalcemia, hypercholesterolemia, hypochloremia, hypomagnesemia, changes in organ weights. Histopathology changes included deposition of calcium in numerous tissues (heart, kidney, lung, trachea, salivary glands, glandular stomach mucosa), parafollicular cell (C-cell) hyperplasia (not recovered in the recovery groups), atrophy of parathyroid cells, thymic atrophy, cytoplasmatic pigmentation of Kupffer cells in the liver, and salivary gland atrophy. The observed NOAEL was ≤ 0.025 µg/kg/day. In a 52-weeks i.v. study (0, 001, 0.02, or 0.04/0.06 µg/kg calcitriol 3-times/week) similar changes were observed.

- Genotoxicity in vitro and in vivo (with toxicokinetics)

Alendronate

There was no evidence for genotoxic potential of alendronate when studied in a standard battery of assays: *in vitro* microbial mutagenesis assay using strains of *E. coli* and *S. typhimurium*, *in vitro*

chromosomal aberration assay, and an *in vivo* chromosomal aberration assay in mice. In an *in vitro* mammalian cell assay, there was a slight increase in the percent cells with chromosomal aberrations at concentration > 5 mM (approximately 1.625 mg/ml), which were considered of no clinical relevance.

Vitamin D_3

Calcitriol was not genotoxic in *in vitro* gene mutation test in bacteria (Ames Test) and one *in vivo* chromosomal aberration test (micronucleus Test) in mice.

- Carcinogenicity (with toxicokinetics)

Alendronate

There was no evidence for carcinogenic potential of alendronate in studies in mice (92 weeks with doses up to 10 mg/kg/day) nor in rats (105 weeks with doses up to 3.75 mg/kg/day).

Vitamin D_3

There are no carcinogenicity data available with vitamin D_3 or its active metabolite in the literature but no studies were considered necessary.

- Reproductive and developmental studies

Alendronate

Alendronate did not affect male rats fertility (NOAEL 9 mg/kg/day). It had no effect on fertility/reproduction in female rats at low doses (NOAEL 2 mg/kg/day). The dose of 5 mg/kg/day caused maternotoxicity (death at the time of delivery), decrease in body weight gain in F1 males during post weaning weeks. There was no effect of behaviour and reproductive performance of F1 pups.
Alendronate was neither embryotoxic nor teratogenic in rats (NOAEL = 5.0 mg/kg/d) and rabbits (NOAEL = 10 mg/kg/d).
Dystocia observed in maternal rats during parturition a class effect of bisphosphonates.

Placental transfer and excretion in milk of alendronate have not been studied in animals.

Vitamin D_3

There are no published studies evaluating the female and male fertility and the developmental toxicity of vitamin D_3 in laboratory animals. The developmental toxicity of 25-hydroxyvitamin D and/or vitamin D_2 has been studied in rabbits and rats. These published data were considered relevant since vitamin D_2 and vitamin D_3 have the same biological activity in humans and both vitamin D_2 and vitamin D_3 are hydroxylated in the liver to 25-0H hydroxyl vitamin D which is the major form of vitamin D in circulation. In rabbits high doses of vitamin D_2 (10.000 or 100.000 IU/animal) during pregnancy affected foetal death, maternal calcium and cholesterol homeostasis and caused calcific aortic lesions and an apparent dose related development of supravalvular aortic lesions in the newborns [12]. In rats it was shown that high doses of vitamin D_2 (20.000 IU/animal; 150.000-200.000 IU/kg/d) given to females prior to mating inhibited pregnancy [13].

- Local tolerance

Alendronate, as a bulk substance, caused irritation to skin and eyes in rabbits. The 5 mg-granulation tablet containing 2.5 % alendronate caused eye irritation but no skin.

There are no available data on local tolerance of vitamin D_3 but no studies were considered necessary.

- Ecotoxicity/environmental risk assessment

Based on an analysis of the environmental risk posed by the use of alendronate, no significant risk to the environment related to the use of the fixed combination is anticipated.

References:

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4. Clinical aspects

Introduction

Alendronate has already been approved as a separate medicinal product in the EU for the treatment of postmenopause osteoporosis. Previous clinical studies have demonstrated the effects of alendronate on bone mass and fracture incidence in postmenopause 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) which 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). In the initial efficacy studies, the mean body bone mineral density (BMD) increases with alendronate 10 mg/day relative to placebo at three years were 8.8 %, 5.9 % and 7.8 % at the spine, femoral neck and trochanter, respectively. Total 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.
In the study FIT1, a three-year study of 2,027 patients who had at least one baseline vertebral (compression) fracture, 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 %). In FIT 2, a four-year study of

4,432 patients with low bone mass but without a baseline vertebral fracture, 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 %).

The therapeutic equivalence of alendronate once weekly 70 mg (n=519) and alendronate 10 mg daily (n=370) was subsequently demonstrated in a one-year multicentre study of postmenopause women with osteoporosis (study 118). 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.

FOSAVANCE combines alendronate at the same 70 mg weekly dose as the one already authorised and vitamin D_3. Consequently, the clinical development programme focused on the demonstration of the bioequivalence between alendronate/vitamin D_3 combination tablet and alendronate 70 mg tablet and on the provision pharmacokinetic data for the vitamin D_3 component of the combination tablet (Study 226). This allows for the bridging with existing efficacy data on alendronate.
No new studies investigating the efficacy of alendronate in terms of bone mass and fracture incidence were therefore conducted.

In the previously conducted pivotal efficacy studies with alendronate, patients received vitamin D supplements. These supplements were however administered at a different time of day from the alendronate tablet, and in the weekly dosing alendronate study, they needed to be taken on days when alendronate tablets were not being given. The data from these previous studies were not sufficient to support the simultaneous administration of alendronate and vitamin D within the same tablet. A new pivotal study was therefore conducted in support of the weekly oral regimen for the treatment of postmenopause osteoporosis with the alendronate/vitamin D_3 combination tablet (Study 227).

All the studies were claimed to have been conducted in accordance with Good Clinical Practices.

Pharmacokinetics

As already mentioned the pharmacokinetics profile of alendronate had previously been assessed. The pharmacokinetic programme consisted therefore of 3 pharmacokinetic studies in support of the weekly oral regimen with the alendronate 70-mg/vitamin D_3 2800-IU combination tablet.
Two pilot studies were conducted prior to the definitive bioequivalence study to gain experience with a new mass spectrometry vitamin D_3 assay to:

- ensure there was no evidence, prior to the definitive study with the proposed formulation, that co-administration with vitamin D_3 affected alendronate bioavailability
- explore the relative bioavailability of alendronate in the combination tablet compared to the 70mg alendronate tablet
- obtain preliminary variability estimates.

The definitive bioequivalence study (Study 226) investigated both alendronate and vitamin D_3 pharmacokinetics, each in a separate part of the study.

A brief summary of the major pharmacokinetic parameters for alendronate is presented below for reference.

The bioavailability of alendronate after oral dosing in human was less than 1 %, similar to that observed in the mouse and rat, and approximately half to that observed in the dog and monkey.
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. 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%. Systematically administered alendronate is tightly sequestered in bone with slightly more sequestration observed in animals (56 % *versus* 60 to 70 %).

Following therapeutic oral doses of alendronate, concentrations in plasma are too low for analytical detection (<5 ng/ml). Protein binding in human plasma is approximately 78%.
As in animals, there is no evidence that alendronate is metabolised in humans.
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 6 hours following intravenous administration. The terminal half-life in humans is estimated to exceed ten years, reflecting release of alendronate from the skeleton. Alendronate is not excreted through the acidic or basic transport systems of the kidney in rats, and thus it is not anticipated to interfere with the excretion of other medicinal products by those systems in humans.

Bioequivalence studies

An outline of the bioequivalence studies is provided in table 1.

Table 1

Study	Design	Objective
Pilot study 183	single dose, open label, randomised, 2-period, crossover study 13 healthy adults (7 males, aged 50-61 years and 7 females, aged 33-54 years)	Bioavailability of alendronate 70 mg tablet with or without vitamin D_3 (5600-IU reconstituted in tap water).
Pilot study 220	single dose, open label, randomised, 3-period, crossover study 12 healthy adults (8 males, aged 24-41 years and 4 females, aged 23-48 years)	To assess: a) the relative bioavailability of alendronate, following administration of the alendronate 70-mg/vitamin D_3 2800-IU combination tablet, relative to the 70 mg alendronate tablet, using cumulative urinary excretion of alendronate over 36 h post-dose, and b) the pharmacokinetics and bioavailability of vitamin D_3 from the alendronate 70-mg/vitamin D_3 2800-IU combination tablet versus a vitamin D_3 2800-IU tablet alone
Definitive bioequivalence study 226	single dose, 2-part, open label, randomised, crossover study 244 healthy adults Part I included 214 adults (95 males, aged 18-64 years and 119 females, aged 18-65 years). Part II included 30 healthy adults (16 males, aged 20-54 years and 14 females, aged 19-48 years)	a) PART I: the relative bioavailability of alendronate following administration of the alendronate 70-mg/vitamin D_3 2800-IU combination tablet, relative to the 70 mg alendronate tablet - based on cumulative urinary excretion over 36 h post-dose b) PART II: the pharmacokinetic and relative bioavailability of vitamin D_3 with the alendronate 70-mg/vitamin D_3 2800-IU combination tablet versus a vitamin D_3 2800-IU tablet alone.

Urinary recovery data, rather than plasma levels, were used to demonstrate bioequivalence of alendronate in the combined tablet compared to alendronate 70 mg tablet, as levels in the blood were too low for accurate delineation of AUC with currently available assays.
Serum concentrations of vitamin D_3 were determined using validated assay with a limit of detection of 0.5 ng/ml.

Results

Pilot study 183

The alendronate total urinary excretion geometric mean ratio, with corresponding 95% confidence intervals (CIs), was 1.16 (0.74, 1.83) for alendronate +vitamin D_3/alendronate alone. These results showed that the relative bioavailability of alendronate was similar with or without concomitant vitamin D_3. The alendronate/vitamin D_3 2800 IU combination tablet was subsequently developed and tested in the second pilot study.

Pilot study 220

The geometric mean ratio, with corresponding 90% CIs, for the urinary excretion of alendronate was 1.02 (0.71, 1.47) for 70-mg alendronate plus 2800-IU vitamin D_3 relative to 70-mg alendronate alone. Thus, the study failed to show bioequivalence according to the accepted 80-125% 90% CI CHMP parameters. These results indicated nonetheless that the relative bioavailability of alendronate was similar in the alendronate 70mg tablet and the combination tablet and that bioequivalence was likely to be demonstrated in a larger, definitive, study.

With regard to vitamin D_3, the AUC0-24h, Cmax and pharmacokinetic profile after administration of the combination tablet are generally similar indicating that alendronate does not affect vitamin D_3 pharmacokinetics. However, serum concentrations of vitamin D_3 had not returned to baseline at the 24 h post-dose time-point, therefore it was concluded that a longer collection period (120h) was needed to fully describe the vitamin D_3 pharmacokinetic profile. This was applied to the definitive Study 226.

Definitive bioequivalence study 226

Part I (for alendronate): The geometric mean ratio, with corresponding 90% CIs, for the total urinary recovery of alendronate /vitamin D_3 2800 IU to 70 mg alendronate alone was 1.03 (0.91, 1.17). Bioequivalence was therefore demonstrated with respect to alendronate between the fixed combination tablet intended for market and the marketed alendronate 70 mg tablet.

Part II (vitamin D_3): The unadjusted-for-baseline endogenous serum vitamin D_3 concentrations single dose pharmacokinetics of vitamin D_3 (AUC0-120h and Cmax) were compared for alendronate/vitamin D_3 2800 IU combination tablet and the 2800 IU vitamin D_3 tablet alone. The results are shown in Table 2. The 90% CI for the Geometric Mean Ratio (GMR) for AUC0-120h and Cmax are within the pre-specified bioequivalence limits of [0.8,1.25].

Table 2: Vitamin D3 pharmacokinetic parameters after single-dose administration of Alendronate 70mg/vitamin D3 2800 IU Combination tablet and a 2800 IU vitamin D3 tablet

Treatment	N	LS Mean	SD	GMR	90% CI for GMR
Vitamin D3 AUC0-120h (ng.h/ml) unadjusted for endogenous vitamin D3 serum concentrations					
70mg alendronate/2800 IU vitamin D3	28	296.4	375.5		
2800 IU vitamin D3 alone	28	337.9	344.2	0.88	0.81, 0.95
Vitamin D3 Cmax (ng/ml) unadjusted for endogenous vitamin D3 serum concentrations					
70mg alendronate/2800 IU vitamin D3	28	5.9	3.3		
2800 IU vitamin D3 alone	28	6.6	3.1	0.89	0.84,0.95
LS = least squares (back transformed from the log scale) *SD = between subject standard deviation (back transformed from log scale)* *GMR = least squares mean ratio (alendronate + vitamin D3/alendronate)* *CI = confidence interval*					

Two alternate methods were used post hoc for sensitivity analyses: (1) ANCOVA with concentration at time 0 hour employed as a covariate and (2) a model-fitted approach which adjusted for baseline serum vitamin D_3 concentrations. These provided similar results (see Table 3). The 90% confidence

intervals for both parameters for the ANCOVA model fell within the standard 80-125% limits for bioequivalence, while the model-based approach did show some reduction of bioavailability of vitamin D3 in the combination tablet relative to the reference vitamin D3 tablet (90% confidence interval (CI) for the geometric mean ratio (GMR) of the AUC combination tablet / reference tablet is (0.76, 0.94). However, this small difference was not considered to have any clinical relevance, as demonstrated by the clinical study (Protocol 227) in which the efficacy of the alendronate / vitamin D_3 combination tablet was demonstrated.

Table 3 Vitamin D3 Pharmacokinetic Parameters After Single-Dose Administrations of an Alendronate/Vitamin D3 2800-IU Combination Tablet and a Vitamin D3 2800- IU Tablet

AUC, Cmax (concentration at time O as covariate) and GMR (90% CI)

	Treatment	N	LS Mean*	SD**	Median	Min	Max	GMR	90% CI for GMR
AUC	Alendronate /vit D3	28	297.5	376.8	257.5	85	1648	**0.88**	**(0.82, 0.95)**
	vitamin D3 Alone	28	336.7	343.0	309.6	111	1485		
Cmax	Alendronate /vit D3	28	5.9	3.3	5.3	2.5	17.48	**0.90**	**(0.85, 0.95)**
	vitamin D3 Alone	28	6.6	3.1	6.2	3.5	18.1		

AUC, Cmax (Model-based vitamin D3 baseline concentration) and GMR (90% CI)

	Treatment	N	LS Mean*	SD**	Median	Min	Max	GMR	90% CI for GMR
AUC	Alendronate /Vit D3	28	143.1	47.7	153.5	61	236	**0.85**	**(0.76, 0.94)**
	Vitamin D3 Alone	28	169.1	37.3	175.0	107	251		
Cmax	Alendronate /Vit D3	28	4.0	1.1	4.0	1.9	6.0	**0.88**	**(0.83, 0.93)**
	Vitamin D3 Alone	28	4.6	0.9	4.6	3.0	7.2		

AUC = ng.h/ml; Cmax = ng/ml;
Root Mean Squared Error (RMSE) = 0.168 (from the ANOVA model).
* Least-square Means back-transformed from the log scale.** Standard Deviation back-transformed from log scale.
GMR=Geometric Mean Ratio (LS mean of vitamin D_3+ alendronate/LS mean of vitamin D_3). CI=Confidence Interval.

Given that the pharmacokinetics profile of alendronate had previously been investigated, and having demonstrated bioequivalence with the currently authorised alendronate 70mg/week dose in healthy subjects, no further pharmacokinetics studies in the target population, special population or to investigate the interaction profile was deemed necessary. All the information relevant to the combination tablet were reflected in the Summary of Product Characteristics.

Pharmacodynamics

The primary and secondary pharmacodynamic actions of alendronate have been previously extensively studied. In summary, the primary effect is on bone mineral density via specific inhibition of osteoclast-mediated bone resorption which arrests and partially reverses the progression of osteoporosis resulting in increased bone mineral density, producing histologically normal bone and decreased fracture incidence. It can therefore be used to reduce the high rate of bone turnover in postmenopause women to a premenopause level. In common with other treatments for osteoporosis, alendronate is always studied in and indicated for the treatment of osteoporosis along with supplemental calcium and/or vitamin D_3 if intake is inadequate.

Vitamin D is the obligate precursor of the active calcium-mobilising hormone – calcitriol (1,25-dihydroxyvitamin D_3). It is an essential nutrient in the typical osteoporotic patient who has little exposure to sunlight and/or lives in the high latitudes of Europe, Northern Asia and North America where there is less potential for exposure to the UBV wavelength required for skin synthesis of vitamin D_3. Calcitriol increases intestinal calcium absorption and is required for healthy bone formation.

No new specific pharmacodynamic studies have been performed with the fixed combination tablet alendronate/vitamin D_3, but markers of bone turnover were incorporated in the main Study 227, whose results are presented in the Clinical efficacy part of this document.

Clinical efficacy

Dose-response studies and main clinical studies

- Dose response study(ies)

The dose of alendronate selected in the fixed combination tablet is 70 mg, which is currently authorised for once weekly treatment of postmenopause osteoporosis.

The rationale for the selected dose of vitamin D_3 in the combination tablet is based on the FDA and Scientific Committee for Food, established by the Commission of the European Communities, which recommends a daily dose of 10µg/day (≡ 400 IU) of vitamin D_3 for all adults (including the elderly and those with inadequate light exposure). It was therefore thought, a 400 IU vitamin D_3 daily dose should be sufficient to ensure adequate vitamin D levels in osteoporotic patients, including those whose supplemental requirements may be greater than average, due to relatively little sunlight exposure and/or little vitamin D in their diet.

Efficacy of vitamin D_3, in terms of maintaining normal levels of 25-hydroxy vitamin D, has been demonstrated in numerous published literature over the last 20 years. Although the findings seemed reasonably consistent, for comparative purposes, these studies are limited by the fact that a variety of vitamin D_3 products were used and potency, stability and bioavailability of these products were rarely reported. Furthermore, none was studied using the proposed dosing schedule of 2800 IU once weekly, to be taken at least 30 minutes before breakfast or other medication.

Given that it was technically not feasible to conduct a study to show that a weekly dose of 2800 IU is bioequivalent to giving 400 IU/day, adequate efficacy of the weekly dose in terms of vitamin D status needed to be proven in order to adequately support the application. The applicant therefore conducted Study 227, described in the section below.

- Main study

Study 227 was a multicentre, randomised, double blind, double dummy, parallel group, active-controlled Phase III study to evaluate the safety, tolerability and efficacy of alendronate 70 mg/vitamin D_3 2800 IU combination tablet in men and postmenopause women with osteoporosis over 15 weeks. The study included a 24 week randomised double active controlled extension.

METHODS

Study Participants

The study was conducted in predominantly postmenopause osteoporotic women and osteoporotic men. Entry criteria were consistent with the current alendronate product information and included those patients in general good health aged between 40 and 90 years with a lumbar spine or hip bone mineral density (BMD T-score ≥ 2.5 SD below the mean for normal premenopause women). 'Postmenopause' was defined as amenorrhoea for ≥ 6 months preceding randomisation [+ endocrine confirmation in non-ovariectomised women <55 years if less than 18 months since last menses].
All patients were required to have serum 25-hydroxyvitamin D level $\geq$ 9 ng/ml. Patients with levels between 9 and 15 ng/ml (cut-off level for vitamin D insufficiency) were required to have a normal parathyroid hormone and alkaline phosphatase.

Treatments

Patients were randomly assigned to receive either alendronate 70mg/vitamin D_3 2800 IU or alendronate 70mg for 15 weeks. A "double-dummy" design was used. All patients received daily supplementation with 500 to 600 mg of elemental Ca++ (as carbonate). If a patient's 25-hydroxyvitamin D level fell below 9 ng/ml, study medication was discontinued, but the patient remained in the study and continued to be followed for safety.

Objectives

The primary objective was to evaluate the efficacy of alendronate 70 mg/vitamin D_3 2800 IU administered once weekly as a combination tablet to reduce the proportion of patients with vitamin D insufficiency in postmenopause women and men with osteoporosis, compared to alendronate 70mg alone after 15 weeks of treatment.

Outcomes/endpoints

The primary efficacy endpoint was the proportion of patients with serum 25-hydroxyvitamin D below the insufficiency threshold of 15 ng/ml at week 15. The applicant justified the choice of serum 25-hydroxyvitamin D <15ng/ml as cut-off point for vitamin D deficiency.

Secondary endpoints included the proportion of patients with serum 25-hydroxyvitamin D below the deficiency cut-point (<9 ng/ml); change from baseline in serum 25-hydroxyvitamin D; the log fraction of baseline value in serum calcium, 24-hour urine calcium, serum Bone Specific Alkaline Phosphatase (BSAP), urine N-telopeptides of Type 1 collagen (NTx), serum phosphate, and serum parathyroid hormone.

Sample size

For the primary hypothesis, a sample size of 340 evaluable patients per treatment group, after 15 weeks of treatment with alendronate/vitamin D3, would have 90% power to detect a difference of at least 11.3% in the combination group (alpha=0.05, two-tailed). This calculation assumed that after 15 weeks of treatment, the 25-hydroxyvitamin D insufficiency (<15 ng/ml) rate would be 35% in the alendronate only group.

Randomisation

Eligible patients were stratified by baseline 25-hydroxyvitamin D level (≥ 9 but <15ng/ml or >15 ng/ml), then randomised by a computer-generated allocation schedule to receive either alendronate/vitamin D_3 2800 IU or alendronate once weekly for 15 weeks

Statistical methods

The primary method used was an All-Patients-Treated (APT) analysis. It included all randomised patients who took at least one dose of study treatment and had at least one post-randomisation measurement. Missing data were inputed by carrying the previous post-randomisation measurement forward. However, since patients whose 25 hydroxyvitamin D_3 levels fell to below 9ng/ml were instructed to treat their vitamin D deficiency with a supplement, measurements taken after the identification of vitamin D deficiency were treated as missing.
For the 15 weeks base study, the efficacy of alendronate/vitamin D_3 2800 IU on low vitamin D rate reduction was evaluated by calculating the proportions of patients with serum 25-hydroxyvitamin D <15ng/ml and comparing the proportions between the combination tablet group and alendronate groups. The comparison was performed using a Cochran-Mantel-Haenszel test adjusted for baseline vitamin D stratum. The test assessed the relative reduction in the proportion of patients with serum 25 hydroxyvitamin D <15ng/ml in the alendronate/vitamin D_3 2800 IU group. The associated 95% CI for the relative risk was provided. In addition, the between-treatment difference of the proportions summarised across strata was estimated with a 95% CI using the weighted average method with Cochran-Mantel-Haenzel weighting strategy. The same testing and estimation techniques were utilised to compare the proportion of patients at week 15 with vitamin D levels <9 ng/ml as the key secondary analysis. As a secondary analysis, a parametric analysis of covariance (ANCOVA) model was used to analyse the treatment effect on changes from baseline at week 15 in serum 25-hydroxyvitamin D levels. The model included factors for baseline serum 25-hydroxy D levels, geographic location and treatment groups. Treatment differences were estimated by differences in least-squares means from the model and their 95% CIs were calculated.

RESULTS

Results at 15 weeks are available.

Participant flow

The study enrolled 717 patients (682 women and 35 men). Of those, 360 were randomised to the alendronate/vitamin D_3 combination tablet and 357 to alendronate tablet.

Of the 717 patients entered into the study, 673 (93.9%) completed; 338 (93.9%) and 335 (93.8%) in the alendronate/vitamin D_3 2800-IU and alendronate treatment groups, respectively. Of the 44 (6.1%) patients who discontinued, 22 (6.1%) received alendronate/vitamin D_3 2800-IU and 22 (6.2%) received alendronate. Reasons for discontinuation included adverse events: 30 (4.1%) of patients overall; 14 (3.9%) in the alendronate/vitamin D_3 2800-IU group and 16 (4.5%) in the alendronate group. Six (0.8%) patients overall discontinued due to protocol deviations; 5 (1.1%) and 2 (0.6%) in the alendronate/vitamin D_3 2800-IU and alendronate treatment groups, respectively. Four (0.6%) patients, 2 (0.6%) in each treatment group, withdrew consent; and 4 (0.6%) patients, 2 (0.6%) in each treatment group, discontinued due to patient move or other reasons.

Baseline data

The patients had a mean age of 66.8 years (range: 35 to 89 years). 98.6% of patients were White, 0.7% Black, 0.6% Hispanic American, and 0.1% Indian. At baseline, there were no clinically meaningful differences between treatment groups with respect to age, calcium intake, vitamin D intake, average BMD (lumbar spine: 0.73 and 0.86 g/cm^2, femoral neck: 0.60 and 0.74 g/cm^2; Hologic and Lunar, respectively) and the average laboratory values. About 95 % of the patients had a T-score $\leq$ - 2.5 for at least one of the T-scores in either femoral neck or lumbar spine total sites (79 % had a lumbar spine T score of $\leq$ - 2.5).

Mean 25-OHD levels at baseline in the two treatment groups were 22.4 ng/ml (median 21 ng/ml, range 9-90 ng/ml) in the alendronate/vitamin D_3 group and 22.3 ng/ml (median 21 ng/ml, range 9-84 ng/ml) in the alendronate group. At baseline, 21% of patients in both treatment groups had serum 25-hydroxyvitamin D levels <15 ng/ml (none had serum 25-OHD concentration of <9 ng/ml; see exclusion criteria).

Efficacy data

The results are displayed in table 4.

At week 15, the proportion of patients with serum 25-hydroxyvitamin D levels <15 ng/ml in the alendronate 70-mg/vitamin D_3 2800-IU treatment group (11 % versus 32 %) was significantly reduced versus the group treated with alendronate alone ($p<0.001$). The relative risk was 0.36 (95% CI: 0.27, 0.48) in those who received alendronate 70-mg/vitamin D_3 2800-IU (relative risk reduction = 64%).

Table 4: Analysis of the proportion of patients with 25 hydroxyvitamin D levels <15 ng/ml (all patients treated population)

Treatment	N	Baseline		On-treatment	
		events	proportion	events	proportion
ALN/VITD	357	76	0.21	41	0.11
ALN	351	75	0.21	112	0.32
Relative risk using Cochran-Mantel-Haenszel test adjusted for baseline stratum					
Between-group comparison		Relative risk	95 % CI for relative risk		p-value
ALN VITD vs ALN		0.36	(0.27, 0.48)		< 0.001
Difference in proportion using weighted average approach with Cochran- Mantel –Haenszel weighting strategy					
Between group comparison		Adjusted rate difference		95 % CI for Adjusted rate difference	
ALN VITD vs ALN		- 0.20		(- 0.25, -0.15)	

Alendronate 70-mg/vitamin D_3 2800-IU also significantly reduced the proportion of patients with vitamin D deficiency (serum 25-hydroxyvitamin D levels <9 ng/ml), compared with patients administered alendronate tablet (secondary efficacy parameter). The proportion of patients with serum 25-hydroxyvitamin D levels <9 ng/ml at Week 15 was 1% in the alendronate 70-mg/vitamin D_3 2800-IU group and 13% in the alendronate 70 mg group. The relative risk was 0.09 (95% CI: 0.03, 0.23) in those who received alendronate/vitamin D_3 2800-IU (relative risk reduction = 91%).

With respect to the change from baseline in serum 25-hydroxyvitamin D, there was a slight increase of average 1 ng/ml in the patients treated with alendronate 70-mg/vitamin D_3 2800-IU (from 22.2 to 23.1 ng/ml) while treatment with alendronate tablet resulted in a decrease of -3.4 ng/ml (from 22.1 to 18.4 ng/ml). The between-group difference of 4.6 ng/ml was significant ($p<0.001$).

The mean changes from baseline 25-OH vitamin D in patients with vitamin D insufficiency (25-OHD < 15ng/ml) were in the alendronate 70-mg/vitamin D_3 2800-IU group (n=76) from 12.1 ± 1.7 ng/ml (at baseline) to 15.8 ± 3.9 ng/ml (SD) at week 15, and in the alendronate tablet group (n=75) from 12.1 ± 1.7 ng/ml (at baseline) to 10.4 ± 4.0 ng/ml (SD) at week 15. In addition, the combination of alendronate 70-mg/vitamin D_3 2800-IU did not fully prevent the development of vitamin D deficiency [alendronate 70-mg/vitamin D_3 2800-IU: 1% (4/357 patients]; alendronate tablet alone: 13% (46/357 patients).

With regard to markers of bone turnover, there was no significant difference between the 2 treatment groups. The means of urine NTx/Cr (bone resorption marker) decreased significantly from baseline at week 15 (53.40% and 53.27%) and the means of serum bone-specific alkaline phosphatase (as bone formation marker) decreased significantly from baseline at week 15 (27.2% and 25.16%) in the alendronate 70-mg/vitamin D_3 2800-IU and alendronate groups, respectively ($p\leq0.001$).
The changes in urine NTX and BSAP were similar to those observed in study 118 (a study previously reported which compared the effects of 10 mg daily, 35- mg twice daily and 70 mg once weekly alendronate in postmenopause women with osteoporosis). Despite some differences in methodology and time points of assay (week 15 in study 227 and 3 month in study 118) the effects on bone turnover are comparable in both studies.
Patients in both treatment groups experienced significant decreases:

- in serum calcium from baseline at Week 15: 0.87% (9.49 to 9.43 mg/dl; $p\leq0.01$) versus 1.38% (9.48 to 9.38 mg/dl; $p\leq0.001$) in the alendronate 70-mg/vitamin D_3 2800-IU and alendronate groups, respectively
- in serum phosphate from baseline at Week 15 (2.37% (3.58 to 3.47 mgP/dl) vs 3.60% (3.61 to 3.45 mgP/dl) in the alendronate 70-mg/vitamin D_3 2800-IU and alendronate groups, respectively ($p<0.001$)).

There was no significant difference between the 2 treatment groups.

Patients in both treatment groups experienced significant increases in serum parathyroid hormone from baseline at Week 15. The increase in the alendronate group was 24.33% (45.46 to 54.65 pg/ml), and the increase in the alendronate/vitamin D_3 2800-IU group was 13.90% (47.35 to 52.47 pg/ml). The mean difference between groups, -10.43 (95% CI -17.57, -3.30), was significant (p=0.004) but small. Subgroup analysis revealed that there was an inverse relationship between 25-OHD levels and PTH levels - the lower the baseline 25-OHD level, the higher was the increase in PTH at the end of study.

The percentage of men included in the study is small (about 4.9%), and the applicant showed that the data from men did not significantly influence the baseline data or the overall outcome in postmenopause women.

The applicant committed to provide longer-term efficacy data from the 24-week double blind extension with the alendronate 70-mg/vitamin D_3 2800-IU combination tablet as a follow-up measure to be fulfilled post-authorisation.

Clinical safety

Safety data for the alendronate 70-mg/vitamin D_3 2800-IU combination tablet derive from the pharmacokinetic studies (Studies 183, 220 and 226) and the main clinical trial (Study 227).
In addition safety data from the previously mentioned 12-month study (Study 118), where women with postmenopause osteoporosis were treated with alendronate 10 mg daily (n=370), 35 mg twice weekly (n=369) and 70 mg once weekly (n=519) are available.

- Patient exposure

In the pharmacokinetic studies, 250 adults were exposed to a single dose of the combination tablet.
In the clinical Study 227, 360 patients with osteoporosis (mean age 66.6 years, range 35-89 years) in the alendronate 70-mg/vitamin D_3 2800-IU group received an average of 14.7 weeks of treatment.

- Adverse events

In all three pharmacokinetics studies, there were no clinically significant changes or trends in vital signs, physical examinations, or ECGs based on visual inspection of the data. One subject in Study226 was discontinued from the study because of a non treatment-related adverse event. There were no serious adverse events, and no subject was discontinued due to a laboratory adverse event.

For Study 22, the summary of adverse events is shown in Table 5 and the most common treatment-related adverse events (occurring in at least 1% of patients in either treatment group) are shown in Table 24. No new treatment-related adverse events were identified and the safety profile of the combination tablet seems to be consistent with that of alendronate alone.

Table 5: Study 227 Summary of adverse events

	Combination tablet N=360		**Alendronate 70mg† N=357**	
	Number of patients	**%**	**Number of patients**	**%**
≥ one Adverse Event	215	59.7	210	58.8
No Adverse Events	145	40.3	147	41.2
With treatment-related Adverse Events	57	15.8	57	16.0
With Serious Adverse Events	7	1.9	15	4.2
With Serious treatment-related* Adverse Events	0	0	1	0.3
Deaths	0	0	0	0
Discontinuation due to Adverse Events	18	5	17	4.8
Discontinuation due to treatment-related* Adverse Events	13	3.6	13	3.6
Discontinuation due to Serious Adverse Events	1	0.3	2	0.6
Discontinuation due to Serious treatment-related* Adverse Events	0	0	0	0
**Treatment related = considered by the investigator to be possibly, probably or definitely treatment-related*				

†*One patient in the alendronate group was dispensed study drug but reported never taking a dose*

The percentage of patients who discontinued due to an adverse event was similar between the two treatment groups with approximately one half of the discontinuations being due to events related to the upper gastrointestinal tract. (1.9 and 2.5% in the combination tablet and alendronate groups, respectively).

Table 6: Study: 227 - Number and %age of patients with treatment-related* adverse events reported with a frequency ≥ 1% by organ system/disease category

MedDRA Disease Category Groupings	**Combination tablet N=360**		**Alendronate 70mg† N=375**	
	Number of patients n	**%**	**Number of patients n**	**%**
≥ one Adverse Event	57	15.8	57	16.0
No Adverse Events	303	84.2	300	84.0
Gastrointestinal	34	9.4	37	10.4
Abdominal pain	3	0.8	4	1.1
Abdominal pain upper	4	1.1	8	2.2
Diarrhoea	4	1.1	3	0.8
Dyspepsia	6	1.7	8	2.2
Nausea	9	2.5	9	2.5
General Disorders and Administration site Conditions	5	1.4	2	0.6
Musculoskeletal and Connective Tissue Disorders	13	3.6	14	3.9
Arthralgia	5	1.4	5	1.4
Bone Pain	1	0.3	5	1.4
Myalgia	5	1.4	4	1.1
Nervous System Disorders	11	3.1	4	1.1
Headache	8	2.2	4	1.1

Although a patient may have had 2 or more adverse events, the patient is counted only once within a category. The same patient may appear in different categories.
† *one patient in the alendronate group was dispensed study drug but reported never taking a dose*
* *classified by the investigator as possibly, probably or definitely drug related*

- Serious adverse event/deaths/other significant events

No deaths were reported in any of the studies.

- In Study 227, serious adverse events occurred slightly more frequently in the combined tablet group (4.2%) compared to the alendronate only group (1.9%), but no serious treatment-related adverse events (classified as possibly, probably or definitely drug related), were reported, except in one patient (0.3%) in the alendronate group– i.e. worsening of a pre-existing anaemia of unknown aetiology which the investigator considered to be possibly related to both study therapy and concomitant warfarin treatment.

Given that irritation of the upper gastrointestinal mucosa is a recognised adverse effect of bisphosphonates these events were specifically examined. The findings were consistent with those of other clinical studies involving alendronate. The exclusion criteria for study 227 included only upper gastrointestinal conditions contraindicating bisphosphonate therapy e.g. oesophageal abnormalities including stricture and achalasia and 365 of patients in the study had a history of other gastrointestinal disorders. Overall, the incidence of upper gastrointestinal events was similar in the two groups (14% and 16% in the combined tablet and alendronate groups, respectively). Treatment-related upper gastrointestinal adverse events occurred in 30 patients (8.3%) in the combined tablet group and 33 patients (9.2%) in the alendronate group. A total of 16 patients discontinued study drug due to upper gastrointestinal adverse events. Two patients developed gastrointestinal serious adverse events that were not considered drug related. Esophageal adverse events occurred in less than 1% of combined tablet and alendronate treated patients.

- *Laboratory findings*

With the exception of some decreases in 25-hydroxyvitamin D level, there were overall no differences in laboratory parameters between the two groups. The majority of the reductions in 25-hydroxyvitamin D levels occurred in the alendronate group (13.1% versus 1.1% in the combined tablet group). Eight events led to discontinuation in the alendronate group (all due to low 25-hydroxyvitamin D). There were no serious laboratory adverse events and drug-related adverse events were infrequent (1.1% and 0.6% in the combination tablet and alendronate groups, respectively). Decreased 25 hydroxyvitamin D was rated as possibly, probably or definitely related to treatment by the investigator in two patients (both in the alendronate group). A review of predefined limits of change for all measured laboratory parameters revealed no between-group differences.

Laboratory adverse events were evaluated specifically for signs of vitamin D toxicity e.g. hypercalcaemia, hypercalciuria. The mean serum Ca++ and urinary Ca++ levels decreased by similar amounts during treatment with both the combined tablet and alendronate - which is attributable to reduced resorption of bone Ca++ by the action of alendronate. Hypercalciuria was not reported and changes in 24-hour urinary Ca++ excretion which exceeded the pre-defined limit of >300mg/day, or an increase >25%, were seen with the same frequency in both groups. Hypercalcaemia was not reported and no significant effect of the combined tablet on serum Ca++ or 24-hour urinary Ca++ excretion was found. As there is a theoretical risk that vitamin D3 may exacerbate hypercalcaemia and/or hypercalciuria when administered to patients with diseases associated with unregulated overproduction of calcitriol (1,25 hydroxyvitamin D) e.g. leukaemia, lymphoma and sarcoidosis, a warning is included in the Summary of Product Characteristics to cover this along with the recommendation to monitor urine and serum Ca++ in these patients.

Post-marketing experience

There are no post-marketing data available for the alendronate 70-mg/vitamin D_3 2800-IU tablet.
Alendronate alone (10mg/day) is marketed in over 90 countries and 70mg/once weekly in over 75 countries. As of June 2004 the cumulative patient-years of experience exceeds 23 million. In post-marketing experience, bone, joint, and/or muscle pain have rarely been severe and/or incapacitating. The time to onset of symptoms varied from one day to several months after starting treatment. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when rechallenged with the same medicinal product or another bisphosphonate. A warning has been included in the Summary of Product Characteristics.

5. Overall conclusions, benefit/risk assessment and recommendation

Quality

Information on development, manufacture and control of the active substances and finished product have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the Summary of Product Characteristics. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Non-clinical pharmacology and toxicology

No pharmacodynamic, pharmacokinetic or toxicology studies have been conducted with the combination of alendronate and vitamin D_3. It was considered that the extensive literature for vitamin D, the comprehensive preclinical data previously obtained for alendronate, and the clinical experience

with the administration of vitamin D_3 as a nutrient supplement with alendronate sodium which did not result in adverse findings in human, superseded the need for additional animal data.

The mode of action of alendronate postulates incorporation of the drug present on the bone surface into the cytoplasm of the osteoclast. Various animal pharmacodynamic analyses show that vitamin D_3 acts as a prohormone that is readily metabolised to 25-OH vitamin D_3 in the liver. The activating step of converting 25-OH vitamin D_3 to the active hormone by the 1α-hydroxylase in the kidney is tightly controlled by circulating levels of PTH, calcitonin and 1α, $25(OH)_2$ vitamin D_3 itself.
Animal studies of the effects of a combination of bisphosphonate with 1α $25(OH)_2$ vitamin D_3 suggest additive effects on bone. This suggests that the mechanism of action of either agent is non-redundant. The combination of vitamin D_3 with alendronate would thus be predicted to have beneficial effects on bone homeostasis that extend beyond the effects elicited by alendronate alone.

The pharmacokinetic properties of alendronate sodium have been extensively evaluated. It is poorly absorbed in animals. Systemically available alendronate disappears very rapidly from plasma, and the compound is either taken up by bone tissues or excreted by the kidney, which is the only elimination pathway. Vitamin D_3 is absorbed by passive diffusion in the intestine as a fat-soluble vitamin, and requires bile salt for optimal absorption. Vitamin D_3 is inactive and requires sequential hydroxylation in the liver and kidney to become the biologically active form, 1α, 25 dihydroxyvitamin D_3. The enzymes that mediate the hepatic and renal metabolism of vitamin D_3 are the mitochondrial CYP27A1 and CYP27B1, respectively. The biologically active form of vitamin D_3 is then metabolically inactivated in a mutistep process. The metabolites of vitamin D_3 appear to be excreted predominantly in bile and subject to enterohepatic recirculation.

Repeated dose toxicity, genotoxicity and carcinogenic studies revealed no special hazard of alendronate for humans. 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.

Calcitriol, a synthetic hormonal metabolite of vitamin D_3 was not mutagenic or genotoxic. In repeat-dose studies treatment-related changes observed with high doses were attributed to exaggerated pharmacologic effect of vitamin D_3. At doses far higher than the human therapeutic range, reproductive toxicity has been observed in animal studies.

Efficacy and safety

No new clinical studies have been conducted to investigate the efficacy of the alendronate component in terms of bone-mineral density were conducted. Instead, the applicant confirmed the bioequivalence (Study 226), of alendronate in the combined tablet, compared to the 70 mg marketed alendronate tablet, and this is considered an acceptable bridge to the existing efficacy data for the latter. The data showed however that the combination tablet is slightly less bioavailable with regard to vitamin D_3.

In support of the weekly oral regimen with the alendronate 70 mg/ vitamin D_3 2800IU combination tablet, a single clinical study was conducted (Study 227). This multicenter study aimed to evaluate the efficacy of alendronate 70mg/vitamin D 2800 IU administered once weekly as a combination tablet to reduce the proportion of patients with vitamin D insufficiency (serum 25-hydroxyvitamin D <15ng/ml) in 682 postmenopause women with osteoporosis, compared to alendronate 70mg alone after 15 weeks of treatment.
At week 15, the proportion of patients with serum 25-hydroxyvitamin D levels <15 ng/ml in the alendronate 70-mg/vitamin D_3 2800-IU treatment group was significantly reduced versus the group treated with alendronate alone ((11% versus 32%, $p<0.001$).
The proportion of patients with serum 25-hydroxyvitamin D levels <9 ng/ml at week 15 was 1% in the alendronate 70-mg/vitamin D_3 2800-IU group and 13% in the alendronate 70 mg group. The relative risk was 0.09 (95% CI: 0.03, 0.23) in those who received alendronate/vitamin D_3 2800-IU (relative risk reduction = 91%).

In terms of safety, alendronate 70 mg/ vitamin D_3 2800IU combination tablet was found to be generally safe and well-tolerated in the target population, with a safety profile which is consistent with that of the marketed alendronate 70mg product. Therefore, the contraindications, warnings and precautions contained in the current alendronate 70mg Summary of Product Characteristics are applicable to the proposed product. With regard to the vitamin D3 component of the combination tablet, there was no evidence of vitamin D toxicity.

The applicant committed to provide longer-term efficacy and safety data from the 24-week double blind extension with the alendronate 70-mg/vitamin D_3 2800-IU combination tablet, as a follow-up measure to be fulfilled post-authorisation.

Benefit/risk assessment

Overall, the clinical data support the conclusions that the combination tablet, compared to alendronate alone, administered once weekly reduces the risk of vitamin D insufficiency (defined as a serum 25 hydroxyvitamin D i.e. serum level 9 to <15ng/ml), reduces the risk of vitamin D deficiency (defined as a serum 25 hydroxyvitamin D i.e. serum level <9 ng/ml), causes an increase in mean serum 25-hydroxyvitamin D – the levels fall on alendronate alone - and results in similar rates of bone resorption (NTx), bone formation (BSAP), serum Ca++, serum phosphate and 24 hour urine Ca++ and is associated with less serum PTH elevation. In terms of safety, alendronate 70 mg/ vitamin D_3 2800IU combination tablet has a safety profile consistent with that of the marketed alendronate 70 mg tablet. FOSAVANCE encompassing the advantage of a fixed dose combination of alendronate 70-mg/vitamin D_3 2800-IU to be taken once weekly has the potential to simplify the treatment of postmenauposal osteoporosis.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered consensus that the benefit/risk ratio of FOSAVANCE was favourable and therefore recommended the granting of the marketing authorisation for the indication: “Treatment of postmenopausal osteoporosis in patients at risk of vitamin D insufficiency. FOSAVANCE reduces the risk of vertebral and hip fractures”.