EU RISK MANAGEMENT PLAN (RMP) FOR Alendronic Acid / Colecalciferol Tablets

RMP version to be assessed as part of this application:

RMP Version number: 8.1

Data lock point for this RMP: 15-JAN-2024

Date of final sign off: 24-SEP-2024

Date of finalization: 24-SEP-2024

Rationale for submitting an updated RMP:

The present Risk Management Plan (RMP) (version 8.1) has been prepared based on the request received from the Committee for Medicinal Products for Human Use (CHMP) within the procedure EMEA/H/C/WS2467 to update the RMP of alendronic acid/colecalciferol to reclassify the risk of atypical femoral fracture from "important potential risk" to "important identified risk" and to extend the risk of "atypical femoral fracture" to "atypical fractures of long bones."

Summary of significant changes in this RMP:

The proposal to change the list of safety concerns and missing information topics is presented based on the GVP V-Rev. 2.0. All sections have been modified based on the new RMP template requirements.

Part	Major changes compared to RMP v 7.1
Part I	Updated to reflect the new template requirements. Marketing Authorization Holder (MAH) details updated.
Part II	**Module SI:** Updated to reflect the new template requirements. Epidemiology data updated. **Module SII:** Updated to reflect the new template requirements. **Module SIII:** Updated to reflect the new template requirements. **Module SIV:** The post-marketing exposure was updated. **Module SV:** Updated to reflect the new template requirements. **Module SVI:** Updated to reflect the new template requirements. **Module SVII:** Updated to reflect the new template requirements. **Removal of the important identified risks:** Oesophageal adverse experiences. Osteonecrosis of the jaw. **Removal of missing information topics:** Use during pregnancy and lactation. Use in patients below 18 years of age. Use in patients with severe renal insufficiency (GFR less than 35 mL/min) **Reclassification**

	Atypical femoral fractures (previously: important potential risk; reclassified to important identified risk and extended to "Atypical fractures of long bones"). **Module SVIII:** Updated to reflect the current list of safety concerns.
Part III	Updated to reflect the new template requirements.
Part IV	Updated to reflect the new template requirements.
Part V	Updated to reflect the new template requirements.
Part VI	Updated to reflect the new template requirements.
Part VII	Updated to reflect the new template requirements.

Other RMP versions under evaluation:

Not applicable

Details of the currently approved RMP:

Version number: 7.1

Approved with procedure:

- For Fosavance: EMEA/H/C/619/R/032
- For Adrovance: EMEA/H/C/000759/IB/0030
- For Vantavo: EMEA/H/C/001180/R/0019

Date of approval (opinion date):

- For Fosavance (EMEA/H/C/619/R/032): 26-FEB-2015
- For Adrovance (EMEA/H/C/000759/IB/0030): 17-DEC-2014
- For Vantavo (EMEA/H/C/001180/R/0019): 24-JUL-2014

QPPV name*:* Fernanda Tavares, MD

QPPV signature: see signature page

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV. The electronic signature is available on file.

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Experience
AFF	Atypical Femoral Fractures
ATC	Anatomical Therapeutic Chemical classification system
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
EEA	European Economic Area
EMA	European Medicines Agency
EMEA	Europe, the Middle East, and Africa
EPAR	European Public Assessment Report
EU	European Union
FSA	Financial Sharing Area
GFR	Glomerular Filtration Rate
GI	Gastrointestinal
GVP	Good Pharmacovigilance Practice
INN	International Nonproprietary Name
IU	International Unit
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
N/A	Not Applicable
NHANES	National Health and Nutrition Examination Survey
ONJ	Osteonecrosis of the Jaw
PAES	Post-authorization Efficacy Study
PSUR	Periodic Safety Update Report
PT	Preferred Term
PV	Pharmacovigilance
PYT	Patient-Years of Treatment
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk Management Plan
SERMs	Selective Oestrogen Receptor Modulators
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Queries
US	United States
WFRS	Worldwide Financial Reporting System
WHO	World Health Organization

PART I: PRODUCT(S) OVERVIEW

Table I.1: Product Overview

Active substance(s) (INN or Generic name)	Alendronic acid / Colecalciferol
Pharmacotherapeutic group(s) (ATC Code)	Bisphosphonates, combinations ATC code : M05BB03
Marketing Authorisation	Marketing Authorization Holder (MAH) and applicant: N.V. Organon Kloosterstraat 6 5349 AB Oss The Netherlands
Number of medicinal products to which this RMP refers	Three (3)
Invented name(s) in the European Economic Area (EEA)	Fosavance, Adrovance, Vantavo
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Alendronic acid (as alendronate sodium trihydrate) – Bisphosphonates Colecalciferol (vitamin D3) - Similar to steroids
	Summary of mode of action: *Alendronate sodium* is a bisphosphonate that inhibits osteoclastic bone resorption with no direct effect on bone formation. Activity of osteoclasts is inhibited, but recruitment or attachment of osteoclasts is not affected. The bone formed during treatment with alendronate sodium is of normal quality. *Colecalciferol* (Vitamin D3) is converted to 25 hydroxyvitamin D3 in the liver and stored until needed. Conversion to the active calcium-mobilizing hormone 1, 25 dihydroxyvitamin D3 (calcitriol) in the kidney is tightly regulated. The principal action of 1,25 dihydroxyvitamin D3 is to increase intestinal absorption of both calcium and phosphate as well as regulate serum calcium, renal calcium, phosphate excretion, bone formation and bone resorption. Vitamin D3 is required for normal bone formation.
	Important information about its composition: 70 mg/2800 IU Tablet *Excipients with known effect:* Each tablet contains 62 mg lactose anhydrous and 8 mg sucrose. 70 mg/5600 IU Tablet *Excipients with known effect:* Each tablet contains 63 mg lactose anhydrous and 16 mg sucrose.
Hyperlink to the Prescribing Information	See latest approved Prescribing information in Module 1.3 from submission EMEA/H/C/XXXX/WS/2467 Fosavance: https://organon-rim.veevavault.com/ui/#permalink=V1W0000000LO035 Adrovance: https://organon-rim.veevavault.com/ui/#permalink=V1W0000000LM055 Vantavo: https://organon-rim.veevavault.com/ui/#permalink=V1W0000000LO036
Indication(s) in the EEA	Current (if applicable): 70 mg/2800 IU Tablet and 70 mg/5600 IU Tablet Treatment of postmenopausal osteoporosis in women at risk of vitamin D insufficiency. The medicinal product reduces the risk of vertebral and hip fractures.
	Proposed (if applicable): Not applicable

Table I.1: Product Overview

Dosage in the EEA	Posology The recommended dose is one Fosavance tablet once weekly. Patients should be instructed that if they miss a dose of Fosavance, they should take one tablet in 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, Fosavance 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 Fosavance on an individual patient basis, particularly after 5 or more years of use. Patients should receive supplemental calcium if intake from diet is inadequate. [*For 70 mg/2800 IU Tablet*: 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 Fosavance to daily dosing of vitamin D 400 IU has not been studied.] *[For 70 mg/2800 IU Tablet*: The equivalence of intake of 5600 IU of vitamin D3 weekly in FOSAVANCE to daily dosing of vitamin D 800 IU has not been studied.] Special populations *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* Fosavance is not recommended for patients with renal impairment in whom glomerular filtration rate (GFR) is less than 35 ml/min due to lack of experience. No dose adjustment is necessary for patients with a GFR greater than 35 ml/min. *Paediatric population* The safety and efficacy of Fosavance in children less than 18 years of age have not been established. Fosavance 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: Fosavance must be taken with water only (not mineral water) at least 30 min 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 sodium. The following instructions should be followed exactly in order to minimize the risk of oesophageal irritation and related adverse reactions: • Fosavance 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 swallow Fosavance 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 min after taking Fosavance. • Fosavance should not be taken at bedtime or before arising for the day.
	Proposed (if applicable): Not applicable (NA)

Table I.1: Product Overview

Pharmaceutical form(s) and strengths	Current (if applicable): 70 mg/2800 IU Tablet Each tablet contains 70 mg alendronic acid as alendronate sodium trihydrate and 70 micrograms (2800 IU) colecalciferol (vitamin D_3). Each tablet is a capsule-shaped, white to off-white tablet, marked with an outline of a bone image on one side, and '710' on the other. 70 mg/5600 IU Tablet Each tablet contains 70 mg alendronic acid as alendronate sodium trihydrate and 140 micrograms (5600 IU) colecalciferol (vitamin D_3). Each tablet is a modified rectangle-shaped, white to off-white tablet, marked with an outline of a bone image on one side, and '270' on the other.
Is/will the product be subject to additional monitoring in the EU?	No

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Indication **: Osteoporosis in postmenopausal women**

SI.1 Epidemiology of the Disease

A recent estimate of the global prevalence of osteoporosis is 18.3%, based on reports from 86 studies across five continents. Although the number of reported epidemiological studies on osteoporosis in Africa is limited, recent studies have shown that osteoporosis and the incidence of related fractures has increased across the continent [Ref. 5.4: 0FHR8C].

Other recent publications have summarized the available literature and highlighted the variability of prevalence estimates both at individual country and continent level (Xiao et al.). In the systematic review and meta-analysis by Xiao and based on World Health Organization (WHO) criteria for diagnosis, national estimates ranged from 4.1% to 52%. An even more recently published review of evidence from the Asia-Pacific region (Chandran et al.) highlighted the availability of data, but with caution expressed over the quality. Nonetheless, estimated prevalence of osteoporosis was 5-10% but with the caveat that this was likely to be an underestimate [Ref.5.4: 0FHR8G], [Ref. 5.4. 0FHR5Y].

Incidence:

No data are available for the incidence of osteoporosis. Incidence rates of hip and vertebral fractures, the major consequences of osteoporosis, are listed below.

Crude incidence of hip fracture in women (per 100,000) by age in European countries is shown in Table SII.1 [Ref.5.4: 03P7M9].

Table SII.1 Crude Incidence of Hip Fracture in Women (per 100,000) by age in European Countries

Country	50-79	80+
Sweden	721	6,033
Portugal*	76	77
Iceland	333	2,267
Switzerland	240	1,973
England	187	1,814
Ireland	213	1,797
Finland	190	1,657
Former GDR	183	1,048
Netherlands	171	1,576
Yugoslavia	-	671
Malta	73	856
Poland	43	250
*Men and women combined GDR = German Democratic Republic		

Incidence of vertebral fractures in women (per 100,000) by age in Europe and the United States (US) is shown in Table SII.2.

Table SII.2 Incidence of Vertebral Fractures in Women (per 100,000) by Age in Europe and the United States

Age	Morphometric Vertebral Fractures in Women		Vertebral Fracture in Women
	Fracture Incidence per 1000 py		Fracture Incidence per 1000 py
	Europe [Ref.5.4:03R369]	US [Ref.5.4: 03R36B]	US [Ref.5.4: 03R36B]
50-54	3.6	0.29	0.64
55-59	5.5	0.57	1.32
60-64	9.5	1.05	1.24
65-69	12.3	2.03	2.33
70-74	17.9	3.94	4.73
75-79	29.3	7.93	5.23
80-84	-	14.47	6.22
85+	-	26.05	10.95
All*	10.7	-	-
*Age standardized to European population			

Prevalence:

In the US, prevalence of osteoporosis in women 65 years of age and older based on testing at the hip in the National Health and Nutrition Examination Survey (NHANES) 1988-1994 is shown in Table SII.3 [Ref. 5.4: 03R374]:

Table SII.3 US Prevalence of Osteoporosis in Women 65 Years of Age and Older Based on Testing at the Hip in the NHANES (1988-1994)

Age Range	Osteoporosis (%)
Female	**26.1**
65-74	19.0
75-84	32.5
85+	50.5

In Norway, age-specific prevalence rates of diagnosed osteoporosis are shown in Table SII.4 [Ref. 5.4: 03R36X]:

Table SII.4 Age-Specific Prevalence Rates of Diagnosed Osteoporosis in Norway

Age Range	Osteoporosis (%)
Female	-
47-50	2.6
61-65	12
71-75	21.8

In addition, osteoporosis prevalence by age in women in Norway is shown in Table SII.5 [Ref.5.4: 03R368]:

Table SII.5 Osteoporosis Prevalence by Age in Women in Norway

Age Range	Osteoporosis (%)
Female (all age groups 30+)	**20.9**
All > 50	22.6
All > 70	35.2

In Sweden, osteoporosis prevalence by age in women is shown in Table SII.6 [Ref.5.4: 03R36R]:

Table SII.6 Osteoporosis Prevalence by Age in Women in Sweden

Age Range	Osteoporosis (%)
50-54	6.3
55-59	9.6
60-64	14.3
65-69	20.2
70-74	27.9
75-79	37.5
80-84	47.2
50-84	**21.2**

Table SII.7 In 2015, the crude fracture rate in Canada was approximately 16 fragility fractures per 1000 persons aged ≥ 50 years

Country/Province	Number of fractures in 2015	Population at risk in 2015 (thousands)	Crude fracture rate/1000	Population growth 2015–2030
Canada	211,968	13,363	16	24%
British Columbia	30,856	1866	17	23%
Alberta	17,027	1271	13	39%
Saskatchewan	8510	389	22	24%
Ontario	76,627	5092	15	26%
Quebec	53,052	3257	16	19%
New Brunswick	5399	327	17	15%
Newfoundland	3654	225	16	18%

Number of fractures and predicted growth in men and women >50Y [Ref.5.4: 0FHR5W]

PPD

Demographics of the population in the authorised indication:

With increasing life expectancy and longevity, the prevalence of osteoporosis and related fractures is increasing**.** [Ref.5.4: 0FHR8C]

Risk factors for the disease:

Osteoporosis originates from loss of bone mass along with microarchitectural deterioration of the skeleton. Bone mass starts decreasing among men and women in their 40s, leading to increased risk of fragility fractures. However, women lose bone more rapidly, particularly during the first 5–10 years after menopause due to estrogen deficiency, while men experience a slow loss of bone. Multiple risk factors are associated with low bone density-related fractures. Significant associations include advancing age, white race, history of prior fractures and genetic factors. Modifiable factors such as increased alcohol consumption and smoking are also prominent. Furthermore, chronic glucocorticoid use, hypogonadism, diabetes, dementia, and rheumatoid arthritis were discussed as secondary causes of osteoporosis in the current review. Many metabolic bone diseases including hyperparathyroidism and osteomalacia also are associated with low bone mineral density. [Ref.5.4: 0FGSQ9]

The main existing treatment options:

Bisphosphonates (such as alendronate sodium, risedronate, zoledronate or ibandronate) are considered the standard treatment options for osteoporosis. Adequate calcium and vitamin D are important for maintaining bone health and for the effectiveness of anti-resorptive therapy. Inadequate vitamin D can result in decreased calcium absorption, increased parathyroid hormone concentrations, and increased bone turnover. Low calcium intake may increase vitamin D metabolism and deplete vitamin D. The need for vitamin D supplement, in addition to alendronate sodium, depends on the vitamin D status and the risk of vitamin D deficiency. People without vitamin D deficiency or obvious risk factors for deficiency are unlikely to benefit from a supplement, and there is no reason to switch such patients from alendronate sodium to the combined formulation. Denosumab is a bone anti-resorptive drug indicated for postmenopausal patients at high risk for fracture or others who have failed, or are intolerant to, other osteoporosis therapies. Selective oestrogen receptor modulators (SERMs) are medicines that have a similar effect on bone as the hormone oestrogen. They help to maintain bone density and reduce the risk of fracture, particularly of the spine. Raloxifene is the only type of SERM available for treating osteoporosis.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Increased morbidity and mortality are associated with osteoporotic hip and vertebral fractures [Ref.5.4: 03Q20Q]. The risk of death is approximately threefold higher among women who have a vertebral or hip fracture [Ref.5.4: 03R36P]. All low-trauma fractures are associated with increased mortality risk for 5-10 years [Ref.5.4: 03R39H]; the highest risk is found immediately after the fracture event [Ref.5.4: 03R36Q].

Important co-morbidities:

Table SII.8 Important Co-morbidities in Patients with Postmenopausal Osteoporosis

<table>
<tr><th>Indication / Target Population</th><th>Cardiovascular Disease</th></tr>
<tr><td>Incidence</td><td>Ten-year incidence rates for cardiovascular events in Caucasian US women with unknown osteoporotic status per 1000 person-years [Ref.5.4: 03R365] are listed below.
<table>
<tr><th>Age (years)</th><th>Coronary heart disease</th><th>Myocardial infarction</th><th>Congestive heart failure</th></tr>
<tr><td>65-69</td><td>16.1</td><td>6.9</td><td>10.7</td></tr>
<tr><td>70-74</td><td>20.2</td><td>9.0</td><td>15.7</td></tr>
<tr><td>75-79</td><td>32.4</td><td>12.8</td><td>26.6</td></tr>
<tr><td>80-84</td><td>34.4</td><td>13.3</td><td>32.8</td></tr>
<tr><td>≥85</td><td>28.3</td><td>21.4</td><td>61.0</td></tr>
<tr><td>Total</td><td>21.8</td><td>9.4</td><td>17.8</td></tr>
</table></td></tr>
<tr><td>Prevalence</td><td>Data specific to postmenopausal women with osteoporosis were not available; however, the following prevalence among women was reported in the American Heart Association 2009 report [Ref.5.4: 03R362]:
<table>
<tr><th>Age (years)</th><th>Coronary heart disease</th><th>Congestive heart failure</th></tr>
<tr><td>60-79</td><td>15.1</td><td>4.8</td></tr>
<tr><td>80+</td><td>23.9</td><td>12.2</td></tr>
</table></td></tr>
<tr><td>Mortality</td><td>Cardiovascular disease is the leading cause of death for American and European women. [Ref.5.4: 03R365], [Ref. 5.4: 03R36W] It was found that women with osteoporosis are at an increased risk of cardiovascular events above that of the general population of postmenopausal women [Ref.5.4: 03R36Z].</td></tr>
</table>

Table SII.8 Important Co-morbidities in Patients with Postmenopausal Osteoporosis

Indication / Target Population	**Stroke**
Incidence	Data specific to postmenopausal women with osteoporosis were not available; however, the following incidence among women was reported: World Health Organization stroke incidence estimates for European women per 100,000 by country [Ref.5.4: 03R370].

	Age category				
Country	**45-54**	**55-64**	**65-74**	**75-84**	**85+**
Austria	69	172	613	1,376	1,801
Belgium	84	186	550	1,237	1,661
Cyprus	40	134	463	1,726	2,753
Czech Republic	119	347	1,449	2,918	3,513
Denmark	80	184	580	1,250	1,628
Finland	74	191	653	1,391	1,784
France	49	109	364	837	1,113
Germany	60	152	588	1,395	1,857
Greece	98	288	1,216	3,312	4,671
Iceland	74	187	647	1,493	1,990
Ireland	99	192	672	1,396	1,732
Italy	63	154	585	1,569	2,214
Luxembourg	103	231	721	1,584	2,087
Malta	81	203	789	1,637	2,021
The Netherlands	93	175	565	1,265	1,657
Norway	69	148	530	1,359	1,887
Portugal	149	390	1,431	3,193	4,153
Spain	57	143	498	1,207	1,647
Sweden	65	164	535	1,287	1,767
Switzerland	49	110	329	822	1,158
UK	94	209	652	1,453	1,925
Estonia	133	407	1,171	2,473	3,284
Latvia	205	587	1,645	3,539	4,757
Hungary	141	332	907	1,680	2,070
Lithuania	138	332	882	1,659	2,081
Poland	103	289	800	1,459	1,792
Slovakia	58	183	631	1,102	1,251
Slovenia	139	296	858	1,754	2,244

Table SII.8 Important Co-morbidities in Patients with Postmenopausal Osteoporosis

Prevalence

Data specific to postmenopausal women with osteoporosis were not available; however, the following prevalence among women was reported:

World Health Organization stroke prevalence estimates for European women per 100,000

	Age category				
Country	**45-54**	**55-64**	**65-74**	**75-84**	**85+**
Austria	634	1,304	3,791	6,807	8,733
Belgium	804	1,476	3,568	6,260	8,362
Cyprus	171	553	1,507	3,112	4,881
Czech Republic	1,103	2,637	8,965	15,171	17,156
Denmark	775	1,484	3,820	6,554	8,342
Finland	695	1,490	4,168	7,148	8,890
France	465	857	2,324	4,218	5,553
Germany	535	1,122	3,524	6,646	8,759
Greece	838	2,037	6,996	14,686	21,217
Iceland	702	1,464	4,140	7,537	9,954
Ireland	1,044	1,708	4,777	8,178	9,681
Italy	548	1,114	3,416	7,038	10,178
Luxembourg	1,022	1,914	4,854	8,441	10,944
Malta	787	1,639	5,167	8,878	10,422
The Netherlands	919	1,464	3,780	6,752	8,681
Norway	589	1,060	3,049	6,060	8,534
Portugal	1,400	3,020	9,038	16,185	20,578
Spain	509	1,061	3,017	5,698	7,805
Sweden	554	1,155	3,090	5,750	7,953
Switzerland	455	847	2,062	3,911	5,639
UK	857	1,589	4,041	7,101	9,288
Estonia	647	2,108	4,772	6,434	6,669
Latvia	984	2,994	6,628	8,994	9,548
Hungary	838	2,037	6,996	14,686	21,217
Lithuania	697	1,769	3,746	4,741	4,402
Poland	661	1,523	3,584	4,920	4,627
Slovakia	349	902	2,617	3,726	3,035
Slovenia	1,418	2,524	5,966	9,760	12,098

Mortality

Stroke is the third leading cause of death in developed countries and second overall worldwide.[Ref.5.4: 03R36Y] Postmenopausal women have an increased risk of stroke. The extent to which hormone status and hormone therapy influence the risk of stroke in postmenopausal women is unclear [Ref.5.4: 03R362].

Indication / Target Population

Chronic obstructive pulmonary disease

Table SII.8 Important Co-morbidities in Patients with Postmenopausal Osteoporosis

<table>
<tr><td>Incidence</td><td>Data specific to postmenopausal women with osteoporosis were not available; however, in a population-based study, the following was reported:

Incidence of Chronic Obstructive Pulmonary Disease (COPD) in women from the Netherlands by age group (n = 4,878) [Ref.5.4: 03R372].

<table><tr><th>Age (years)</th><th>COPD per 1000 py (95% CI)</th></tr><tr><td>55-59</td><td>7.4 (4.1-12.6)</td></tr><tr><td>60-64</td><td>3.3 (2.0-5.1)</td></tr><tr><td>65-69</td><td>7.4 (5.7-9.5)</td></tr><tr><td>70-74</td><td>10.0 (8.0-12.3)</td></tr><tr><td>75-79</td><td>8.4 (6.5-10.6)</td></tr><tr><td>≥80</td><td>2.9 (2.1-3.9)</td></tr></table></td></tr>
<tr><td>Prevalence</td><td>Data specific to postmenopausal women with osteoporosis were not available; however, in a population-based study, the following was reported:

Prevalence of COPD in Spanish women by age group (n = 3,802) [Ref. 5.4: 03R36T]

<table><tr><th>Age (years)</th><th>COPD % (95% CI)</th></tr><tr><td>50-59</td><td>4.4 (2.8-6.1)</td></tr><tr><td>60-69</td><td>7.5 (5.0-10.0)</td></tr><tr><td>70-80</td><td>10.7 (7.3-14.1)</td></tr></table></td></tr>
<tr><td>Mortality</td><td>Chronic obstructive pulmonary disease was ranked the sixth leading cause of death worldwide in 1990 and the fourth leading cause of morbidity [Ref.5.4: 03R372].</td></tr>
<tr><td>Indication / Target Population</td><td>Vitamin D deficiency</td></tr>
<tr><td>Incidence</td><td>No data are available.</td></tr>
</table>

Table SII.8 Important Co-morbidities in Patients with Postmenopausal Osteoporosis

Prevalence

Vitamin D deficiency is defined as a 25-hydroxyvitamin D level of less than 20 ng/mL and vitamin D insufficiency as a level between 20-30 ng/mL [Ref. 5.4: 03QDDB]. Prevalence at 25(OH) D cut-off points in postmenopausal women (ages 41-96 years) with osteoporosis [Ref. 5.4: 03R3XL].

Country / region	(n)	Mean age (years)	<15 ng/mL (%)	<20 ng/mL (%)	<30 ng/mL (%)
Europe	(1,020)	68.4	11.7	23.8	57.7
Sweden	(150)	70.2	3.3	12.7	37.3
United Kingdom	(98)	70.3	28.6	40.8	74.5
Germany	(100)	70.2	15.0	33.0	68.0
The Netherlands	(50)	67.8	8.0	18.0	52.0
France	(199)	67.1	8.1	16.2	49.7
Switzerland	(173)	68.5	14.1	30.7	63.3
Hungary	(100)	65.2	4.0	16.0	56.0
Spain	(150)	67.5	14.0	24.7	64.7
Middle East	(401)	65.1	38.2	57.9	81.8
Turkey	(150)	61.0	31.3	57.3	76.7
Lebanon	(251)	67.5	34.3	58.2	84.9
Asia	(549)	67.3	13.1	34.1	71.4
South Korea	(101)	65.9	36.6	64.4	92.1
Japan	(198)	68.4	13.6	47.0	90.4
Thailand	(100)	67.1	2.0	12.0	47.0
Malaysia	(150)	67.0	4.0	11.3	48.7
Latin America	(415)	65.5	7.2	21.5	53.4
Mexico	(149)	65.6	8.1	29.5	67.1
Brazil	(151)	67.6	6.0	15.2	42.4
Chile	(115)	62.6	7.8	19.1	50.4
Australia	(204)	67.5	7.8	23.0	60.3
All countries	(2,589)	67.1	14.3	30.8	63.9

Prevalence at 25-hydroxyvitamin D cut-off points in postmenopausal women (mean age 71.1 years) with osteoporosis (n = 1,536) [Ref. 5.4: 03PT7F]

Country / region	<20 ng/mL	<30 ng/mL
North America	18.2	52.0

Mortality

Data specific to postmenopausal women with osteoporosis are not available. However, within a group of all adults of 20 years and older from NHANES III (n = 13,331), the lowest quartile of 25-hydroxyvitamin D level (<17.8 ng/mL) was associated with all-cause mortality and increased with age. Women with 25-hydroxyvitamin D levels < 20 ng/mL also had an increased rate of mortality. [Ref. 5.4: 03R36S].

Concomitant Medication(s) in the Target Population

Concomitant medications as per the co-morbidities observed in the target population are as follows:

Cardiovascular Disease: Antianginal medications (e.g. nitrates), antiplatelet agents (acetylsalicylic acid and anticoagulants), beta blockers, lipid-lowering agents (statins, fenofibrate, niacin, bile acid sequestrants and cholesterol absorption inhibitors [ezetimibe]).

Stroke: Antiplatelet agents (e.g. aspirin and anticoagulants)

Chronic Obstructive Pulmonary Disease (COPD): Bronchodilators, beta-agonists (e.g. albuterol, metaproterenol, pirbuterol, terbutaline and isoetharine), beta-2 agonists (e.g. levaibuterol, salmeterol and formoterol fumarate), anti-cholinergic agents (e.g. ipratropium bromide and tiotropium), methylxanthines (e.g. theophylline and aminophylline), corticosteroids (e.g. prednisone, prednisolone, beclomethasone dipropionate, triamcinolone acetonide, fluticasone, budesonide, mometasone furoate, flunisolide and salmeterol) phosphodiesterase-4 inhibitors (rofumilast) and oxygen.

Vitamin D Deficiency: Vitamin D supplements, increased consumption of vitamin D-rich foods (e.g. fish, liver, and processed milk).

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from non-clinical studies and relevance to human usage:

Table SII.9: Summary of Important Safety Findings from Non-clinical Studies

Key Safety Findings (from non-clinical studies)	Relevance to Human Usage
Oesophageal adverse experiences In rats, high doses (30 mg/kg/day) of alendronate sodium orally resulted in gastric erosion and ulceration; the no-observed-effect level was 10 mg/kg/day. In dogs, oral administration of alendronate sodium resulted in no gastrointestinal (GI) irritation. However, daily oesophageal exposure (30 min) to alendronate sodium (0.2 mg/mL; pH 2.0) resulted in mucosal irritation, whereas once-a-week exposure at four times the concentration (0.8 mg/mL; pH 2.0) resulted in no evidence of oesophageal irritation after four weekly treatments in dogs. The observations in rats and dogs are similar to finding with compounds in this class.	**Oesophageal adverse experiences** The animal studies have shown that alendronate sodium has the potential to cause gastric oesophageal and gastric GI irritation given daily at high doses. This concern was carefully evaluated during the clinical development programme through adverse event review and studies that included upper GI endoscopy as a safety endpoint.
Renal toxicity Renal changes, usually mild without any renal function impairment, were observed histologically in dogs given daily doses greater than 2 mg/kg/day.	**Renal toxicity** No significant human risk: No renal toxicity has been associated with oral alendronate sodium use in either clinical trials or through review of marketed-use adverse event reports.
Reproductive and developmental toxicity Reproduction studies in rats showed decreased post-implantation survival at 2 mg/kg/day and decreased body weight gain in normal pups at 1 mg/kg/day. Sites of incomplete foetal ossification were statistically significantly increased in rats beginning at 10 mg/kg/day in vertebral (cervical, thoracic, and lumbar), skull, and sternebral bones. The above doses ranged from one time (1 mg/kg) to ten times (10 mg/kg), the maximum recommended daily dose of 10 mg/day based on surface area (mg/m^2). No similar foetal effects were seen when pregnant rabbits were treated at doses up to 35 mg/kg/day (40 times a 10 mg human daily dose based on surface area [mg/m^2]). Both total and ionized calcium decreased in pregnant rats at 15 mg/kg/day (13 times a 10 mg human daily dose based on surface area [mg/m^2]) resulting in delays and failures of delivery. Protracted parturition due to maternal hypocalcaemia occurred in rats at doses as low as 0.5 mg/kg/day (0.5 times a 10 mg human daily dose based on surface area [mg/m^2]) when rats were treated from before mating through gestation. Maternal toxicity (late pregnancy deaths) occurred in the female rats treated with 15 mg/kg/day for varying periods of time ranging from treatment only during pre-mating to treatment only during early, middle, or late gestation; these deaths were lessened but not eliminated by cessation of treatment. Calcium supplementation either in the drinking water or by minipump could not ameliorate the hypocalcaemia or prevent maternal and neonatal deaths due to delays in	**Reproductive and developmental toxicity** The theoretical risk for either maternal or foetal harm in humans is related to both current and prior use of bisphosphonates. 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. In theory, risk can result from either maternal hypocalcaemia/hypophosphataemia or direct foetal exposure to the drug. It is unknown whether alendronate sodium crosses the placenta. There are no data on foetal risk in humans. There are no studies of alendronate sodium in pregnant women. No adverse reproductive effects have been detected in women who became pregnant during a study of alendronate sodium. Further, review of post-marketing reports of exposure to alendronate sodium during pregnancy has not identified foetal anomalies that could be attributed to the drug exposure.

Table SII.9: Summary of Important Safety Findings from Non-clinical Studies

delivery; calcium supplementation IV prevented maternal, but not foetal, deaths.	
Colecalciferol	**Colecalciferol**
Reproductive and developmental toxicity No data are available for colecalciferol (vitamin D_3). Administration of high doses (≥10000 IU/every other day) of ergocalciferol (vitamin D_2) to pregnant rabbits resulted in abortions and an increased incidence of foetal aortic stenosis. Administration of vitamin D_2 (40,000 IU/day) to pregnant rats resulted in neonatal death, decreased foetal weight, and impaired osteogenesis of long bones postnatally.	**Reproductive and developmental toxicity** There are no studies of alendronate sodium / vitamin D_3 in pregnant women. No adverse reproductive effects of vitamin D_3 would be expected.

The drug is indicated for use in postmenopausal women. No additional non-clinical studies have been conducted or are planned to support the use of alendronic acid / colecalciferol in special populations other than postmenopausal women.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

Alendronic acid /colecalciferol is indicated for the treatment of postmenopausal osteoporosis in women at risk of vitamin D insufficiency.

Alendronate sodium is a bisphosphonate with a well-characterized and established safety profile based on extensive clinical trial experience comprising 45 clinical trials.

Data for the three largest Phase III trials of alendronate sodium (PN051-FIT, PN051-20 FLEX, and PN 227 Phase III alendronate sodium 70 mg once weekly) are presented in the following sections. For the majority of alendronate sodium legacy trials, data are not available in the MAH CTS (Clinical Trial System).

The pre-approval clinical development programme for alendronate sodium / colecalciferol combination tablet consisted of four clinical pharmacology studies (P183, P220, P226, and P253) and one clinical efficacy study (P227).

Overall, the cumulative duration of exposure for all doses of alendronate sodium in all clinical studies is approximately 34,000 patient-years (py). The estimated duration of exposure for the 10 mg daily dose is approximately 13,000 py; for the 70 mg once-weekly dose (administered alone) is approximately 4000 py; for the 70 mg once-weekly dose administered in combination with vitamin D_3 2800 IU is approximately 400 py (from the base study and extension of P227); and for the 70 mg once-weekly dose administered in combination with vitamin D_3 5600 IU (from the extension phase of P227) is approximately 145 py.

Two more clinical studies (PN262 and PN263) were completed. In PN262, there were approximately 233 py of exposure to alendronate sodium 70 mg / colecalciferol 5600 IU. In PN263, 171 patients received alendronate sodium 70 mg / colecalciferol 5600 IU, and 170 patients received alendronate sodium 70 mg weekly for up to 16 weeks.

Phase I Studies of the Combination Tablet

PN183 investigated administration of alendronate sodium 70 mg and vitamin D_3 5600 IU concomitantly as 2 separate products in 14 patients. P220 was a pilot study in 12 patients using the low-dose combination tablet. In P220 and P226, approximately 250 patients were exposed to a single dose of the low-dose combination tablet, and in P253, approximately 300 patients were exposed to a single dose of the high-dose combination tablet.

Phase II-III Studies

Presented below is the exposure to alendronate sodium by duration, dose, age, gender, and race / ethnicity in PN051-FIT (Tables SIII.1, SIII.5, SIII.9 and SIII.13) and PN051-20 FLEX (Tables SIII.2, SIII.6, SIII.10 and SIII.14) clinical trials followed by details of exposure to alendronate sodium / colecalciferol in Protocol 227. In Protocol 227, ‘low-dose combination tablet’ refers to patient who took 2800 IU vitamin D_3 weekly (Tables SIII.3, SIII.7, SIII.11 and SIII.15), and ‘high-dose combination tablet’ refers to patients who received 2800 IU vitamin D_3 plus an additional tablet containing 2800 IU of vitamin D_3 (Tables SIII.4, SIII.8, SIII.12 and SIII.16).

Table SIII.1: Clinical Trial Exposure to Alendronate Sodium by Duration of Exposure (Protocol 051-FIT)

Cumulative for All Indications (Person Time)		
Duration of Exposure	**Patients**	**Person Time (in years)**
Osteoporosis, Postmenopausal		
0 Day	3,236	10,634.3
>6 Months	3,009	10,590.2
>1 Year	2,952	10,547.2
>2 Year	2,811	10,338.2
>3 Year	1,993	8,075.1
>4 Year	1,184	5,107.5
>5 Year	0	0.0
Total person time	55,292.50	

Table SIII.2: Clinical Trial Exposure to Alendronate Sodium by Duration† of Exposure (Protocol 051-20 FLEX)

Minimum Exposure	Randomized, Blinded Trial	
	Persons	**Person-time (in years)**
Osteoporosis, Postmenopausal		
0 Day	662	2,697.5
>6 Months	643	2,692.1
>1 Year	617	2,672.2
>2 Year	569	2,601.1
>3 Year	529	2,501.1
>4 Year	478	2,319.3
>5 Year	77	388.5

†Protocol 051-20 FLEX is an extension of Fracture Intervention Trial (FIT), and the exposure by duration data does not include the time while the patient was on FIT.

Table SIII.3: Clinical Trial Exposure to Alendronate Sodium / Colecalciferol by Duration of Exposure (Protocol 227-Low-dose Combination Tablet)

Minimum Exposure	Randomized, Blinded Trial	
	Persons	Person-time (in years)
Osteoporosis and Vitamin D Deficiency		
0 Day	522	249.0
>1 Week	514	248.1
>6 Weeks	505	247.6
>12 Weeks	493	245.6
>24 Weeks	205	143.1
>36 Week	154	117.0

Table SIII.4: Clinical Trial Exposure to Alendronate Sodium / Colecalciferol by Duration of Exposure (Protocol 227-High-dose Combination Tablet)

Minimum Exposure	Randomized, Blinded Trial	
	Persons	Person-time (in years)
Osteoporosis and vitamin D deficiency		
0 Day	326	146.7
>1 Week	323	146.6
>6 Weeks	322	146.1
>12 Weeks	319	146.0
>24 Weeks	94	45.9

Clinical Trial Exposure by Dose

Table SIII.5: Clinical Trial Exposure to Alendronate Sodium by Dose (Protocol 051-FIT)

Dose of Exposure	Randomized, Blinded Trials	
	Persons	Person-time (in years)
Osteoporosis, Postmenopausal		
5 mg	3,235	5,704.8
10 mg	2,877	4,929.3

Table SIII.6: Clinical Trial Exposure to Alendronate Sodium by Dose (Protocol 051-20 FLEX)

Dose of Exposure	Randomized, Blinded Trials	
	Persons	Person-Time (in years)
Osteoporosis, Postmenopausal		
5 mg	3,235	5,704.8
10 mg	2,877	4,929.3

Table SIII.7: Clinical Trial Exposure to Alendronate Sodium / Colecalciferol by Dose (Protocol 227-Low-dose Combination Tablet)

Dose of Exposure	Randomized, Blinded Trials	
	Persons	Person-time (in years)
Osteoporosis and vitamin D deficiency		
MK-0217A 1 cnt	522	249.0
MK-0217A 2 cnt	1	0.0

Table SIII.8: Clinical Trial Exposure to Alendronate Sodium / Colecalciferol by Dose (Protocol 227-High-dose Combination Tablet)

Dose of Exposure	Randomized, Blinded Trials	
	Persons	Person-time (in years)
Osteoporosis and vitamin D deficiency		
MK-0217A 1 cnt	326	146.7
MK-0217A 2 cnt	2	0.0

Table SIII.9: Clinical Trial Exposure to Alendronate Sodium by Age and Gender (Protocol 051-FIT)

Age Group	Randomized Trial			
	Persons		Person-time (in years)	
	M	F	M	F
Osteoporosis, Postmenopausal				
18-64	0	934	0.0	3,224.8
≥65	0	2,302	0.0	7,409.3

Table SIII.10 Clinical Trial Exposure to Alendronate Sodium by Age and Gender (Protocol 051-20 FLEX)

Age Group	Randomized, Blinded Trial			
	Persons		Person-time (in years)	
	M	F	M	F
Osteoporosis, Postmenopausal				
18-64	0	52	0.0	243.0
≥65	0	610	0.0	2,454.5

Table SIII. 11 Clinical Trial Exposure to Alendronate Sodium / Colecalciferol by Age and Gender (Protocol 227-Low-dose Combination Tablet)

Age Group	Randomized, Blinded Trial			
	Persons		Person-time (in years)	
	M	F	M	F
Osteoporosis and vitamin D deficiency				
18-64	16	188	7.7	87.5
≥65	8	310	4.9	148.4

Table SIII.12 Clinical Trial Exposure to Alendronate Sodium / Colecalciferol by Age and Gender (Protocol 227-High-dose Combination Tablet)

Age Group	Randomized, Blinded Trial			
	Persons		Person-time (in years)	
	M	F	M	F
Osteoporosis and vitamin D deficiency				
18-64	7	123	3.4	56.1
≥65	5	191	2.3	84.8

Clinical Trial Exposure by Racial / Ethnic Origin

Table SIII.13 Clinical Trial Exposure to Alendronate Sodium by Ethnic Origin (Protocol 051-FIT)

Minimum Exposure	Randomized Trial	
	Persons	Person-time (in years)
Osteoporosis, Postmenopausal		
White	3,136	10,293.6
Black	17	57.7

Table SIII.13 Clinical Trial Exposure to Alendronate Sodium by Ethnic Origin (Protocol 051-FIT)

Minimum Exposure	Randomized Trial	
	Persons	Person-time (in years)
Asian	41	151.2
Hispanic American	29	88.6
Multiracial	13	43.3

Table SIII.14 Clinical Trial Exposure to Alendronate Sodium by Ethnic Origin (Protocol 051-20 FLEX)

Minimum Exposure	Randomized, Blinded Trial	
	Persons	Person-time (in years)
Osteoporosis, Postmenopausal		
White	649	2,640.6
Black	2	9.1
Asian	6	28.3
Hispanic American	5	19.5
Multiracial	0	0.0

Table SIII.15 Clinical Trial Exposure to Alendronate Sodium / Colecalciferol by Ethnic Origin (Protocol 227-Low-dose Combination Tablet)

Minimum Exposure	Randomized, Blinded Trial	
	Persons	Person-time (in years)
Osteoporosis and vitamin D deficiency		
White	514	245.1
Other	8	3.1

Table SIII.16 Clinical Trial Exposure to Alendronate Sodium / Colecalciferol by Ethnic Origin (Protocol 227-High-dose Combination Tablet)

Minimum Exposure	Randomized, Blinded Trial	
	Persons	Person-time (in years)
Osteoporosis and vitamin D deficiency		
White	332	144.9
Other	4	1.6

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Table SIV.1.1: Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Exclusion Criterion	Reason for Exclusion	Is it Considered to be Missing Information?	Rationale (if not Included as Missing Information)
Population hypersensitive to bisphosphonate therapy	This population cannot be treated with Fosavance because expected allergic reactions to alendronate sodium may led to serious and / or life-threatening events.	No	This is a contraindication in the EU Summary of Product Characteristics (SmPC).
Population with abnormalities of the oesophagus and other factors which delay oesophageal emptying such as stricture or achalasia	There is a contraindication on Fosavance to not treat this population due to the high risk of worsening of these pathologies.	No	This is a contraindication in the EU Summary of Product Characteristics (SmPC).
Inability to stand or sit upright for at least 30 min	There is a contraindication on Fosavance to not treat this population due to the high risk of worsening of oesophageal pathologies. Patients who are unable to stand or sit upright for at least 30 min are at an increased risk of oesophageal adverse experiences.	No	This is a contraindication in the EU Summary of Product Characteristics (SmPC).
Hypocalcaemia	There is a contraindication on Fosavance not to treat this population due to the high risk of worsening of hypocalcaemia.	No	This is a contraindication in the EU Summary of Product Characteristics (SmPC).
Renal insufficiency	Impaired renal function may decrease the capability of patients to complete the trial.	Yes Use in patients with severe renal insufficiency (GFR <35mL/min) is considered missing information.	N/A
Concomitant disease of bone or mineral metabolism	The clinical trial studies focused on treatment of postmenopausal osteoporosis with oestrogen deficiency and ageing.	No	Listed in the Special warnings and precautions for use of the EU Summary of Product Characteristics (SmPC).

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Program

Fosavance-related osteonecrosis of the jaw (ONJ) and atypical femoral fracture are rare (≥ 1/10,000 to < 1/1,000) bisphosphonate class adverse reactions. Clinical trial studies are limited by sample size; therefore, it is difficult to identify these adverse events during or after the

study. These adverse events are identified in post-marketing experience, though the data are still limited.

Table SIV.2.1: Limitations of Clinical Trial Programme

Ability to Detect Adverse Reactions	Limitation of Trial Programme	Discussion of Implications for Target Population
Which are rare (it may be appropriate to choose other adverse drug reaction [ADR] frequencies)	A total of 550 subjects were exposed to a single dose of the combination of alendronate sodium / colecalciferol in Phase I clinical trials. A total of 848 subjects were exposed to the combination of alendronate sodium / colecalciferol in Phase 2 and Phase 3 clinical trials.	This sample size is not enough to allow the detection of rare adverse experiences (AEs) occurring with a frequency of at least 1 in 10,000.
Due to prolonged exposure	Because the treatment duration with the combination of alendronate sodium / colecalciferol was limited to up to 39 weeks in clinical trials, lifetime clinical exposure data do not exist.	Not applicable
Due to cumulative effects	Not applicable	Not applicable
Which have a long latency	Not applicable	Not applicable because it has been previously studied in alendronate monotherapy trials.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Program

Table SIV.3.1: Exposure of Special Populations Included or not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development program. There have been no reports of pregnancy in patients exposed to alendronate sodium / colecalciferol in clinical studies.
Breastfeeding women	
Patients with relevant comorbidities:	
• Patients with hepatic impairment	Not included in the clinical development program.
• Patients with renal impairment	Not included in the clinical development program. As noted in the European Union (EU) Summary of Product Characteristics (EUSPC) for use in renal impairment, no dosage adjustment is necessary for patients with GFR greater than 35 mL/min. Alendronate sodium is not recommended for patients with renal impairment where GFR is less than 35 mL/min, due to lack of experience.
• Patients with cardiovascular impairment	Not included in the clinical development program.

Table SIV.3.1: Exposure of Special Populations Included or not in Clinical Trial Development Programs

• Immunocompromised patients	Not included in the clinical development program.
• Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program.
Population with relevant different ethnic origin	See table SIII.13 and SIII.14 above.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program
Other	
• Patients who are not postmenopausal osteoporotic women	Studied only to a limited degree.
• Patients with glucocorticoid-induced osteoporosis	Studied only to a limited degree.
• Men with osteoporosis	Studied only to a limited degree.
• Patients below 18 years of age	Alendronate sodium has been studied in a small number of patients with osteogenesis imperfect under 18 years of age. Results are insufficient to support its use in children.

PART II: MODULE SV - POST-AUTHORIZATION EXPERIENCE

SV.1 Post-Authorisation Exposure

SV.1.1 Method Used to Calculate Exposure

A summary of the worldwide distribution of alendronate sodium + colecalciferol for the cumulative period from market introduction to 15-JAN-2024 is presented below. This estimation was based upon the assumption of once-weekly dosing; therefore, the units distributed were divided by 52 weeks to calculate patient-years of treatment (PYT). Patient exposure estimates were calculated from the company's internal distribution data from the Worldwide Financial Reporting System (WFRS), and the Financial Sharing Area (FSA) databases.

SV.1.2 Exposure

Table SV.1.2.1 Patient Exposure

Dosage Distributed and Patient Years of Treatment
Alendronate Sodium + Colecalciferol

Strength	**Distribution[1]** (total number of tablets)	**Patient-Years of Treatment[2]**
	Cumulative to 15-JAN-2024[2]	**Cumulative to** 15-JAN-2024[2]
70 mg/2800 IU	518,697,645	9,974,955
70 mg/5600 IU	538,717,743	10,359,957
Fosamax Plus D + Cal (70/140 mg + 500)	2,761,408	53,104
Total[3]	**1,060,176,796**	**20,388,015**
	Data Source: Worldwide Financial Reporting System (WFRS) from (Formerly Merck, Sharp & Dohme and legacy MSD) and FSA (Organon) [1]The estimate of patient exposure from market introduction is based on the availability of monthly drug distribution figures; hence, this estimate has been calculated from market introduction to 31-DEC-2023, rather than from market introduction to 15-JAN-2024 data-lock point (DLP). [2]Patient-years of treatment = Number of units / 52 weeks [3]Due to rounding the sum of individual corporations may not equal the	

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for Misuse for Illegal Purposes

Alendronic acid / colecalciferol tablet is available only through prescribing physicians. Neither Alendronate acid / colecalciferol nor its components are known to possess addictive properties. It is not a drug with known psychotropic, mood-altering, myoanabolic or analgesic properties. Therefore, it is highly unlikely that it will be sought for illegal use.

The MAH has not been made aware of any reports for misuse for illegal purposes.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

Not applicable

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable

SVII.2 New Safety Concerns and Reclassification With a Submission of an Updated RMP

The list of important safety concerns in the alendronic acid / colecalciferol EU RMP has been revised following Good Pharmacovigilance Practice (GVP) Module V, Rev. 2.0. The updates to the alendronic acid + colecalciferol important identified/potential risks and missing information, along with the rationale for each proposed change, are described in the table below.

Safety concern	Previous classification	Proposed Update	Rationale
Oesophageal adverse experiences.	Important identified risk	Removal	Alendronic acid / colecalciferol is a mature product with over 18 years of post-marketing experience. Oesophageal adverse experiences are secondary to local irritation of the upper gastrointestinal mucosa caused by bisphosphonates and are well-known risk of this therapeutic class. The risk is well characterized in the label and adequately communicated with potential risk factors and risk minimization measures, described in sections 4.2, 4.3, 4.4, and 4.8 of the SmPC. The PSUR data over the last decade shows a downward trend in reporting oesophageal adverse events; new aspects of the known characteristics of this risk have not been identified from continuous monitoring. There are no outstanding or planned additional pharmacovigilance (PV) activities, and routine risk minimization measures are adequate to mitigate the risk of oesophageal adverse experiences.
Osteronecrosis of the jaw.	Important identified risk	Removal	Alendronic acid / colecalciferol is a mature product with over 18 years of post-marketing experience. Osteonecrosis of the jaw is a well-known risk that has also been observed with other bisphosphonates. The risk is well characterized in the label and adequately communicated with potential risk factors and risk minimization measures, described in sections 4.4 and 4.8 of the SmPC.

Safety concern	Previous classification	Proposed Update	Rationale
			The PSUR data over the last decade shows a downward trend in reporting osteonecrosis of the jaw; a targeted follow-up questionnaire is used to ensure adequate reporting of related or precipitating events. New aspects of the known characteristics of this risk have not been identified from continuous monitoring. There are no outstanding or planned additional PV activities, and routine risk minimization measures are adequate to mitigate the risk of osteonecrosis of the jaw.
Atypical femoral fractures.	Important potential risk	Re-classified to important identified risk and extended to "Atypical fractures of long bones."	Atypical femoral fractures (AFF) are a well-known risk that has also been observed with long-term use of other bisphosphonates. Atypical fractures in other bones show similar features to those seen in AFF and described by the American Society for Bone and Mineral Research task force in 2013 (e.g., diaphyseal, atraumatic, or with minimal trauma, non-comminuted, transverse, etc.). Like AFF, atypical fractures of other long bones have shown a tendency to delayed fracture healing, making surgical treatment the preferred therapeutic approach [Ref. 5.4: 0FGV80]. These clinical similarities suggest that atypical fractures are a single risk affecting different types of bone tissue across multiple locations. A recent cumulative literature review for publications concerning alendronic acid, bisphosphonates, and low-energy fractures identified 2,191 citations. Fifty-three case reports of fractures in other long bones were identified in these publications (ulna: 28 fractures, metatarsus: 13 fractures, tibia: 8 fractures, humerus: 2 fractures, radius: 2 fractures. Atypical femur fractures and atypical fractures of other bones are well characterized in the current SmPC and adequately communicated with main clinical characteristics, precipitating factors, and risk minimization measures described in sections 4.4 and 4.8 of the SmPC. The CHMP issued a positive opinion on 30-NOV-2023, under the regulatory procedure, EMEA/H/C/WS2467, to update the SmPC to include information regarding atypical fractures of other long bones, together with a recommendation to update the RMP of alendronic acid + colecalciferol to reclassify the risk of atypical femoral fracture from "important potential risk" to "important identified risk" and to extend the risk of "atypical femoral fracture" to "atypical fractures of long bones." No changes to the overall benefit-risk balance of the product were noted within the CHMP opinion. Atypical fractures (femur and other bones) are being closely monitored through routine PV activities, including the use of a targeted follow-up questionnaire to ensure adequate reporting of fracture events and PSUR systematic reviews of post-marketing reports of atypical periprosthetic femoral fractures and atypical fractures at sites other than the femur.

Safety concern	Previous classification	Proposed Update	Rationale
			There are no outstanding or planned additional PV activities or risk minimization measures.
Use during pregnancy and lactation.	Missing information	Removal	The SmPC currently notes that alendronic acid + colecalciferol is intended for use in postmenopausal women and, therefore, should not be used during pregnancy or in breastfeeding women. Additionally, it is mentioned that it is unknown whether alendronate or its metabolites are excreted in human milk. A review of the Company´s global safety database to identify spontaneous and non-interventional study reports of pregnancy and lactation with alendronate and alendronate / colecalciferol was performed cumulatively until 15-JAN-2024, using the Medical Dictionary for Regulatory Activities (MedDRA) narrow Standardised MedDRA Queries (SMQ) *Pregnancy and neonatal topics.* The search identified 368 cases reporting 610 events (377 serious, 233 nonserious). The three most frequently reported PTs were *Maternal exposure during pregnancy* (140 cases, reporting 215 events), *Exposure during pregnancy* (172 cases, reporting 173 events), and *Maternal exposure timing unspecified* (78 cases, reporting 78 events). Within the *Maternal exposure during pregnancy* reports, the three most frequently co-reported events were *Systemic lupus erythematosus* (120 cases, reporting 126 events), *Alopecia* (119 cases, reporting 121 events), and *Drug ineffective* (118 cases, reporting 121 events). There were 250 prospective reports and 74 retrospective reports; in 44, the report type was not specified. The pregnancy outcome was reported in 15 cases as live birth (14) and live birth premature (1). The fetal outcome was reported in six cases as normal (2), congenital anomaly (2), and perinatal complication (2). The cases reporting “congenital anomaly” and “perinatal complication” merely mentioned these as the fetal outcome without additional details. No clinically relevant safety information has been obtained from the continuous monitoring of use during pregnancy and lactation. There are no outstanding or planned additional PV activities and no reasonable expectation that future PV activities could further characterize the missing information of use during pregnancy and lactation. The information regarding use in pregnancy and use in lactation is well described in the SmPC, is adequately managed by the current routine risk minimization measures and will continue to be monitored via routine pharmacovigilance.
Use in patients below 18 years of age.	Missing information	Removal	The SmPC currently notes that alendronic acid / colecalciferol should not be given to children and adolescents less than 18 years of age. A review of the Company´s global safety database to identify spontaneous and non-interventional study reports was performed cumulatively until 15-JAN-2024 for patients below 18 years of age who were prescribed alendronate and/or alendronate sodium + colecalciferol. The search identified 337 cases reporting 927 events (200 serious, 727 nonserious).

Safety concern	Previous classification	Proposed Update	Rationale
			The three most frequently reported PTs were *Off label use* (75 cases, reporting 77 events), *Product administered to patient of inappropriate age* (48 cases, reporting 48 events), and *Product use in unapproved indication* (44 cases, reporting 44 events). The three most frequently co-reported events within the *Off label use* reports were *Product administered to patient of inappropriate age* (11 cases, reporting 11 events), *Femur Fracture* (4 cases, reporting 8 events), and *Fall* (3 cases, reporting 6 events). The three most frequently co-reported events within the *Product administered to patient of inappropriate age* reports were *Off label use* (11 cases, reporting 11 events), *No adverse event* (3 cases, reporting 3 events, and *Product use in unapproved indication* (3 cases, reporting 3 events). The three most frequently co-reported events within the *Product use in unapproved indication* reports were *Product use issue* (20 cases, reporting 20 events), *Product administered to patient of inappropriate age* (3 cases, reporting 3 events), and *Bone callous excessive* (1 case, reporting 1 event). No clinically relevant safety information has been obtained from the continuous monitoring of use in patients below 18 years of age. There are no outstanding or planned additional PV activities and no reasonable expectation that future PV activities could further characterize the missing information of use in patients below 18 years of age. The information regarding use in pediatric population is adequately managed by the current routine risk minimization measures and will continue to be monitored via routine pharmacovigilance.
Use in patients with severe renal insufficiency (GFR less than 35mL/min).	Missing information	Removal	The SmPC currently notes that alendronic acid / colecalciferol should not be given to patients with renal impairment where creatinine clearance is less than 35ml/min. A review of the Company´s global safety database to identify spontaneous and non-interventional study reports was performed cumulatively until 15-JAN-2024 for patients reporting at least one preferred term (PT) within the MedDRA narrow SMQs *Acute renal failure and chronic kidney disease* as concurrent or historical conditions who were prescribed alendronate and/or alendronate sodium + colecalciferol. The search identified 818 cases reporting 5,145 events (1,174 serious, 3,371 nonserious). The five most frequently reported PTs were *Osteonecrosis of the jaw* (102 cases, reporting 102 events), *Femur fracture* (60 cases, reporting 88 events), *Fall* (54 cases, reporting 74 events), *Osteoarthritis* (46 cases, reporting 63 events), and *Arthralgia* (51 cases, reporting 61 events). No clinically relevant safety information has been obtained from the continuous monitoring of use in patients with severe renal insufficiency. There are no outstanding or planned additional PV activities and no reasonable expectation that future PV activities could further characterize the missing

Safety concern	Previous classification	Proposed Update	Rationale
			information of use in patients with severe renal insufficiency. The information regarding use in in patients with severe renal insufficiency is adequately managed by the current routine risk minimization measures and will continue to be monitored via routine pharmacovigilance.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Table SVII.3.1.1: Details of Important Identified Risk: Atypical fractures of long bones

Identified Risk	Atypical fractures of long bones
Potential mechanisms	The pathophysiology of atypical fractures of long bones in patients taking bisphosphonates has not been completely elucidated. However, the long-term use of bisphosphonates may lead to the suppression of bone turnover, resulting in increased susceptibility, impaired bone remodeling ability, microdamage, and delayed healing of atraumatic, nonpathological stress fractures. Based on a review of additional case reports of atypical fractures in other bones, it is possible that alendronate may have a similar effect on other bones. [0FF7F7], [0FF7F2], [0FF7CT], [0FF7CV], [0FF7CP], [0FF7CQ], [0FF7CR], [0FF7CM], [0FF7CN], [03R678].
Evidence source(s) and strength of evidence:	Post-marketing data, literature reports.
Characterisation of the risk	**Clinical Trials** **Frequency***:* The frequency of femoral fractures has been reported in the FIT of alendronate sodium and its extension (FLEX)[a]. See table below. There is no data regarding other long bones fractures in the FIT and FLEX studies.

	FIT			FLEX		
Fracture Site	ALN (n = 3,236)	PBO (n = 3,223)	RH (95% CI)	ALN* (n = 662)	PBO (n = 437)	RH (95% CI)
Any hip	30	46	0.6 (0.4, 1.0)	21	13	1.1 (0.5, 2.2)
Fem. Neck	16	31	0.5 (0.3, 0.9)	10	7	1.0 (0.4, 2.5)
Intertroch	13	14	0.9 (0.4, 2.0)	10	5	1.3 (0.5, 3.9)
Shaft or Diaphysis	1	1	0.7 (0.04, 11)	2	1	1.3 (0.1, 14)
Distal Metaphysis	1	1	1.0 (0.1, 16)	0	0	NA

RH = Relative hazard; NA = Too few events to estimate RH; ALN = Alendronate; PBO: Placebo
*Pooled 5 mg and 10 mg doses

[a] Bauer D, Black D, Genant H, DePapp A, Santora A, Ensrud K K, et al. Sites of Femoral Fractures in the Fracture Intervention Trial (FIT) of Alendronate and its Long-term Extension (FLEX).

Table SVII.3.1.1: Details of Important Identified Risk: Atypical fractures of long bones

Seriousness / Outcomes

Femoral fractures and fractures of other long bones may require hospitalization and orthopaedic surgery to stabilize the fracture. Atypical femoral fractures (AFF) and atypical fractures of other long bones have shown a tendency for delayed fracture healing, making surgical treatment the preferred therapeutic approach. [0FGV80].

Severity and Nature of the risks:

The American Society for Bone and Mineral Research (ASBMR) task force in 2013 defined the major and minor features of atypical femoral fractures. They recommended that for a case to be considered an atypical femoral fracture, the fracture must be located along the femoral diaphysis, from just distal to the lesser trochanter to just proximal to the supracondylar flare, and 4 of the 5 major features need to be present. The minor features have commonly been described in cases of atypical femoral fractures but are not present in all patients. The CHMP has agreed on a modified case definition that lists "non-comminuted" as a minor feature rather than a major feature of atypical femoral fractures. Atypical fractures in long bones have shown similar features to those seen in AFF and described by the ASBMR.

Background Incidence/Prevalence:

United States incidence prior to oral bisphosphonates:
Incidence of femoral fractures per 100,000 PY in Rochester, Minnesota women by age and type between 1965 and 1984[a].

Age (years)	Subtrochanteric	Diaphyseal
55-64	7.0	8.6
65-74		20.7
75-84	33.9	18.8
≥85	74.2	74.2

- For those patients ≥ 65 years, 65% of fractures were due to low / moderate trauma; includes typical and atypical fractures (no radiographic review to confirm atypical features).

Finland incidence prior to oral bisphosphonates:
Incidence of femoral fractures per 100,000 PY in Finish women from hospital data between 1985-1994[b]

Age (years)	Diaphyseal
55-64	3
65-74	8
75-84	13
≥85	40

United States incidence in a population with ~20.7% exposed to oral bisphosphonates in year prior to index fracture:
Incidence of femoral fractures per 100,000 PY in US women aged 50+ from Market Scan medical claims database between 2002-2006[c].

[a] Arneson TJ, Melton LJ III, Lewallen DG, O'Fallon WM. Epidemiology of diaphyseal and distal femoral fractures in Rochester, Minnesota, 1965-1984. Clin Orthop Relat Res 1988;234:188-94.

[b] Salminen ST, Pihlajamaki HK, Avikainen VJ, Bostman OM. Population based epidemiologic and morphologic study of femoral shaft fractures. Clin Orthop 2000;372:241-9.

[c] Nieves JW, Bilezikian JP, Lane JM, Einhorn TA, Wang Y, Steinbuch M, et al. Fragility fractures of the hip and femur: incidence and patient characteristics. Osteoporos Int 2010;21:399-408.

Table SVII.3.1.1: Details of Important Identified Risk: Atypical fractures of long bones

Year	Subtrochanteric	Diaphyseal
2002	10	13
2003	10	13
2004	12	14
2005	12	13
2006	9	13

Denmark incidence using National Hospital Discharge Register from 1996-2005, untreated with bisphosphonates (mean age 69.8 years):
Incidence of subtrochanteric or diaphyseal fractures per 100,000 PY*[a]

	Subtrochanteric	Diaphyseal
Women	79	57
Men	40	26

*Based on discharge diagnosis only; includes typical and atypical subtrochanteric and diaphyseal fractures; no radiographic review was performed to confirm atypical features.

United States incidence using Kaiser Permanente Northwest Database from 1996-2009 in older men and women, about 30% dispensed 1 or more bisphosphonate prescription:

Incidence of radiographically confirmed atypical subtrochanteric or diaphyseal fractures with major features per 100,000 PY (95% CI) [Feldstein A, report to European Medicinal Agency (EMA), US Food and Drug Administration (FDA), MAR-2011]

Incidence of Radiographically confirmed atypical subtrochanteric or diaphyseal fractures with major features per 100,000 PY (95% CI) [Feldstein A, report to EMA, FDA, MAR-2011]

	Atypical Subtrochanteric or Diaphyseal Fractures with Major Criteria*
Women	6.2 (4.8, 8.0)
Men	4.8 (2.6, 8.0)

*Radiographically confirmed to meet ASBMR criteria for atypical fractures (Major criteria)

United States gender-specific incidence using Kaiser Permanente Northwest Database from 1996-2009 about 30% dispensed 1 or more bisphosphonate prescription:

Year	Atypical Subtrochanteric or Diaphyseal Fractures with Major Features*
1996	2.6 (0.3,9.5)
1997	5.1 (1.4,13.1)
1998	4.9 (1.3,12.6)
1999	3.6 (0.7, 10.5)
2000	5.8 (1.9, 13.6)
2001	8.9 (3.8,17.6)
2002	10.7 (5.1,19.7)
2003	3.1 (0.6, 9.1)
2004	5.1 (1.6,11.8)
2005	8.7 (4.0, 16.4)
2006	9.3 (4.4, 17.0)
2007	3.7 (1.0, 9.4)
2008	3.6 (1.0, 9.3)

[a] Abrahamsen B, Eiken P, Eastell R. 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(12):5258-65.

Table SVII.3.1.1: Details of Important Identified Risk: Atypical fractures of long bones

	<table><tr><td>2009</td><td>7.0 (1.9, 17.9)</td></tr><tr><td>OVERALL</td><td>5.9 (4.6, 7.4)</td></tr></table> *Radiographically confirmed to meet ASBMR criteria for atypical fractures (Major criteria). **Sweden incidence (per 100,000 PY) in women 55 years and older not previously exposed to bisphosphonates using National Swedish Patient Register in 2008**[a]. Incidence of radiographically confirmed atypical subtrochanteric fracture per 100,000 PY. <table><tr><th></th><th>Atypical Subtrochanteric Fracture*</th></tr><tr><td>Women</td><td>0.9</td></tr></table> *Based on radiographic review, met criteria for lateral cortical thickening and transverse on the lateral side consistent with a stress fracture. No studies addressing rates of incidence/prevalence of other long bones have been identified after an extensive search. **Post-marketing:** Cumulatively to 15-Jan-2024 there have been 1,442 case reports of Atypical femoral fractures and 1,238 case reports describing fractures in locations other than the femur. Of these 1,238 fracture case reports, the more commonly affected sites were humerus (n=256), tibia (n=232), pelvis (n=207), and foot (n=134). Of these 1,238 reports of fractures in other locations, 850 were atraumatic or associated with minimal trauma. Eleven cases met most atypical fracture criteria (4 or 5), sufficient to be categorized within the ASBMR classification.
Risk Factors and risk groups	Osteoporosis is the main risk factor for fractures in the older population. Established clinical risk factors for low-energy osteoporotic fractures include advancing age, previous fractures, glucocorticoid therapy, parental history of hip fractures, low body weight, current cigarette smoking, excessive alcohol consumption, rheumatoid arthritis, and secondary osteoporosis (e.g., hypogonadism or premature menopause, malabsorption, chronic liver disease, and inflammatory bowel disease)[bcdefgh]. Known risk factors for stress/insufficiency fractures established in observational studies include prior stress fractures, poor bone health (osteopenia and osteoporosis), substantial increases in the intensity and volume of activities, decreased physical fitness levels, dietary disorders (e.g., low calcium intake and eating disorders), family history of osteopenia or osteoporosis, poor body biomechanics, female gender, and prolonged glucocorticoid

[a] Schilcher J, Michaëlsson K, Aspenberg P. Bisphosphonate use and atypical fractures of the femoral shaft. N Engl J Med 2011;364(18):1728-37.

[b] Kumm DA, Rack C, Rütt J. Subtrochanteric stress fracture of the femur following total knee arthroplasty. J Arthroplasty 1997;12(5):580-3.

[c] World Health Organization. FRAX - WHO Fracture Risk Assessment Tool. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK. http://www.shef.ac.uk/FRAX [accessed 27-Jan-2010]

[d] Kay LJ, Holland TM, Platt PN. Stress fractures in rheumatoid arthritis: a case series and case-control study. Ann Rheum Dis 2004;63:1690-2.

[e] Reynolds MT. Stress fractures of the tibia in the elderly associated with knee deformity [abridged]. Proc Roy Soc Med 1972;65:5-8

[f] Kanis JA, Oden A, Johnell O, Jonsson B, De Laet C, Dawson A. The burden of osteoporotic fractures: A method for setting intervention thresholds. Osteoporos Int 2001;12:417-27.

[g] Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E. FRAX™and the assessment of fracture probability in men and women from the UK. Osteo Int 2008;19:385-97.

[h] Kanis JA, Borgstrom F, De Laet C, Johansson H, Johnell O, Jonsson B, et al. Assessment of fracture risk. Osteo Int 2005;16:581-9.

Table SVII.3.1.1: Details of Important Identified Risk: Atypical fractures of long bones

	use[abcdefg]. Based on the review of the MAH post-marketing reports, co-morbidities and concomitant medications that may have placed patients at risk for developing atypical fractures included rheumatoid arthritis, osteoarthritis and associated musculoskeletal complications, diabetes mellitus, secondary osteoporosis, vitamin D deficiency, changes in the patient's level of physical activity, hormonal deficiencies, and prolonged use of estrogen, glucocorticoids, and proton-pump inhibitors.
Preventability	Preventative measures against femoral fractures and fractures of other bones should focus on the effective treatment of osteoporosis and fall prevention in the elderly. In some literature reports describing low-energy insufficiency fractures of the femur and other bones, thorough evaluation of prodromal pain is recommended for timely identification and management of possible stress reactions or fractures. In patients who have sustained a femoral fracture, the contralateral femur should be examined for possible cortical stress reactions that could progress to complete fractures if untreated. In cases of ulna fracture, this may be associated with repetitive stress loading associated with the long-term use of walking aids.
Impact on the risk-benefit balance of the product:	The impact on individual patients has not been formally evaluated. The risk of atypical fractures in the femur and atypical fractures of other bones is appropriately communicated through the current labeling. No additional risk minimization measures are considered necessary. The benefit-risk balance is considered positive.
Public health impact	Atypical femoral fractures have less public health impact than hip and other typical osteoporotic femoral fractures due to a much lower rate of occurrence, estimated as 1% the incidence of hip and other typical osteoporotic femoral fractures in patients > 75 years of age[b]. In a large national Swedish inpatient study, women were admitted for a median duration of 9 days with femoral fractures and typically required orthopaedic surgery[h]. No studies providing estimates of frequency for atypical fractures in other bones are available, and the number of post-marketing reports of atypical fracture at sites other than the femur is low. Therefore, no significant impact public health impact is expected.

SVII.3.2 Presentation of the Missing Information

There is no missing information in the alendronic acid / colecalciferol EU RMP.

[a] Loud KJ, Micheli LJ, Bristol S, Austin SB, Gordon CM. Family history predicts stress fracture in active female adolescents. Pediatrics 2007;120(2):e364-e372.

[b] Frusztajer NT, Dhuper S, Warren MP, Brooks-Gunn J, Fox RP. Nutrition and the incidence of stress fractures in ballet dancers. Am J Clin Nutr 1990;51(5):779-83.

[c] Bennell KL, Malcolm SA, Thomas SA, Wark JD, Brukner PD. The incidence and distribution of stress fractures in competitive track and field athletes: A Twelve-Month Prospective Study. Am J Sports Med 1996;24(2):211-7.

[d] Bennell KL, Malcolm SA, Thomas SA, Reid SJ, Brukner PD, Ebeling PR, et al. Risk factors for stress fractures in track and field athletes: A twelve-month prospective study. Am J Sports Med 1996;24(6):810-8.

[e] Matheson GO, Clement DB, Mckenzie DC, Taunton JE, Lloyd-Smith DR, Macintyre JG. Stress fractures in athletes: a study of 320 cases. Am J Sports Med 1987;15(1):46-58.

[f] Mattila VM, Niva M, Kiuru M, Pihlajamaki H. Risk factors for bone stress injuries: A follow-up study of 102,515 person-years. Med Sci Sports Exerc 2007;39(7):1061-6.

[g] Rauh MJ, Macera CA, Trone DW, Shaffer RA, Brodine SK. Epidemiology of stress fracture and lower-extremity overuse Injury in female recruits. Med Sci Sports Exerc 2006;38(9):1571-7.

[h] Weiss RJ, Montgomery SM, Al Dabbagh Z, Jansson K-Å. National data of 6409 Swedish inpatients with femoral shaft fractures: stable incidence between 1998 and 2004. Injury Int J Care Injured 2009;40:304-8.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table SVIII.1: Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	Atypical fractures of long bones
Important potential risks	None
Missing information	None

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

The MAH maintains systems and standard practices for routine pharmacovigilance activities to collect reports of suspected adverse reactions (including spontaneous reports, reports from clinical studies, reports of pregnancy/lactation exposures, overdoses and medication errors); prepare reports for regulatory authorities (e.g. individual case safety reports, PSURs, etc.), and maintain continuous monitoring of the safety profile of approved products (including signal detection, issue evaluation, updating of labeling, and liaison with regulatory authorities). The MAH maintains a Pharmacovigilance System Master File which contains details of these systems and standard practices.

Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection:

Specific Adverse Reaction Follow-Up Questionnaire for Atypical Fractures of long bones: Routine PV is planned to closely monitor these events, including event-specific questionnaires sent to reporters of fractures to collect structured information on reported cases. The form is provided in Annex 4.

Other Forms of Routine Pharmacovigilance Activities for Atypical Fractures of long bones: Interval reviews of periprosthetic atypical femoral fractures and atypical fractures (excluding atypical femoral fractures) will be provided in the PSUR.

III.2 Additional Pharmacovigilance Activities

There are no ongoing or planned additional pharmacovigilance activities proposed for alendronic acid / colecalciferol.

III.3 Summary Table of Additional Pharmacovigilance Activities

Not Applicable.

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

There are no ongoing or proposed post-authorization efficacy studies (PAES) for alendronic acid / colecalciferol.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

V.1 Routine Risk Minimization Measures

Table V.1.1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Atypical fractures of long bones	**Routine risk communication** Section 4.4 and Section 4.8 of the SmPC and section 2 of the PIL. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Clinical picture, imaging features and the mention that atypical fractures have been reported primarily in patients with long-term treatment with bisphosphonates are included in section 4.4.

V.2 Additional Risk Minimization Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product

V.3 Summary of Risk Minimization Measures

Table V.3.1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
Atypical fractures of long bones	**Routine risk minimisation measures** SmPC: Section 4.4 and 4.8 Package leaflet: Section 2. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Event specific follow-up questionnaire. PSUR interval reviews of events of interest. **Additional pharmacovigilance activities:** None

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT

Summary of risk management plan for Fosavance (Alendronic acid / Colecalciferol)

This is a summary of the risk management plan (RMP) for Fosavance. The RMP details important risks of Fosavance, how these risks can be minimised, and how more information will be obtained about Fosavance's risks and uncertainties (missing information).

Fosavance's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Fosavance should be used.

This summary of the RMP for Fosavance should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Fosavance's RMP.

I. The Medicine and What it is Used for

Fosavance is authorised for the treatment of postmenopausal osteoporosis in women at risk of vitamin D insufficiency. It reduces the risk of vertebral and hip fractures (see SmPC for the full indication). It contains alendronic acid (as sodium trihydrate) and colecalciferol (vitamin D3) as the active substance and it is given by oral route.

Further information about the evaluation of Fosavance's benefits can be found in Fosavance's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage [link to product's EPAR summary landing page on the EMA webpage].

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Fosavance, together with measures to minimise such risks and the proposed studies for learning more about Fosavance 's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation measures*.

In addition to these measures information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of Important Risks and Missing Information

Important risks of Fosavance are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Fosavance. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table II.A.1: List of Important Risks and Missing Information

List of Important Risks and Missing Information*	
Important identified risks	Atypical fractures of long bones
Important potential risks	None
Missing information	None
*The important identified or potential risks included in prior versions of the RMP have been removed based the review of accumulating clinical data and the guidance in GVP module 5 (Rev 2), as per routine updates of the RMP during the life cycle of the product	

II.B Summary of Important Risks

Table II.B.1: Important Identified Risk – Atypical Fractures of long bones

Evidence for linking the risk to the medicine	Post-marketing data, literature reports.
Risk factors and risk groups	Osteoporosis is the main risk factor for fractures in the older population. Established clinical risk factors for low-energy osteoporotic fractures include advancing age, previous fractures, glucocorticoid therapy, parental history of hip fractures, low body weight, current cigarette smoking, excessive alcohol consumption, rheumatoid arthritis, and secondary osteoporosis (e.g., hypogonadism or premature menopause, malabsorption, chronic liver disease, and inflammatory bowel disease)[abcdefg]. Known risk factors for stress/insufficiency fractures established in observational studies include prior stress fractures, poor bone health (osteopenia and osteoporosis), substantial increases in the intensity and volume of activities, decreased physical fitness levels, dietary disorders (e.g., low calcium intake and eating disorders), family history of osteopenia or osteoporosis, poor body biomechanics, female gender, and prolonged glucocorticoid use[hijklmn]. Based on the review of the MAH post-marketing reports, co-morbidities and concomitant medications that may have placed patients at risk for developing atypical fractures included rheumatoid arthritis, osteoarthritis and associated musculoskeletal complications, diabetes mellitus, secondary osteoporosis, vitamin D deficiency, changes in the patient's level of physical activity, hormonal deficiencies, and prolonged use of estrogen, glucocorticoids, and proton-pump inhibitors.
Risk minimisation measures	**Routine risk minimisation measures** SmPC: Section 4.4 and 4.8 Package leaflet: Section 2.

[a] Kumm DA, Rack C, Rütt J. Subtrochanteric stress fracture of the femur following total knee arthroplasty. J Arthroplasty 1997;12(5):580-3.

[b] World Health Organization. FRAX - WHO Fracture Risk Assessment Tool. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK. http://www.shef.ac.uk/FRAX [accessed 27-Jan-2010]

[c] Kay LJ, Holland TM, Platt PN. Stress fractures in rheumatoid arthritis: a case series and case-control study. Ann Rheum Dis 2004;63:1690-2.

[d] Reynolds MT. Stress fractures of the tibia in the elderly associated with knee deformity [abridged]. Proc Roy Soc Med 1972;65:5-8

[e] Kanis JA, Oden A, Johnell O, Jonsson B, De Laet C, Dawson A. The burden of osteoporotic fractures: A method for setting intervention thresholds. Osteoporos Int 2001;12:417-27.

[f] Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E. FRAX™and the assessment of fracture probability in men and women from the UK. Osteo Int 2008;19:385-97.

[g] Kanis JA, Borgstrom F, De Laet C, Johansson H, Johnell O, Jonsson B, et al. Assessment of fracture risk. Osteo Int 2005;16:581-9.

[h] Loud KJ, Micheli LJ, Bristol S, Austin SB, Gordon CM. Family history predicts stress fracture in active female adolescents. Pediatrics 2007;120(2):e364-e372.

[i] Frusztajer NT, Dhuper S, Warren MP, Brooks-Gunn J, Fox RP. Nutrition and the incidence of stress fractures in ballet dancers. Am J Clin Nutr 1990;51(5):779-83.

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[k] Bennell KL, Malcolm SA, Thomas SA, Reid SJ, Brukner PD, Ebeling PR, et al. Risk factors for stress fractures in track and field athletes: A twelve-month prospective study. Am J Sports Med 1996;24(6):810-8.

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Table II.B.1: Important Identified Risk – Atypical Fractures of long bones

	Additional risk minimisation measures: None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

II.C Post-Authorisation Development Plan

II.C.1 Studies Which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Fosavance.

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for Fosavance.

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ANNEX 4 – SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

This annex contains the specific adverse event targeted follow-up questionnaire to collect additional data for the risk of atypical fractures of long bones.

ORGANON **FOSAMAX/FOSAVANCE AND REPORT OF FRACTURE**

OARS #: [case_num]

[Date]

[Reporter first name and Last name]
[Reporter address]
[Reporter city], [Reporter state], [Reporter postal code]

Dear [Reporter First name and Last name],

We have been notified of a report concerning an event of interest following an exposure to an Organon LLC product.

Patient Name / Initial	[Patient Name] / [Patient Initials]
Age	[Patient Age]
Gender	[Patient Gender]
Product (All Organon suspect products)	[Insert all products separated by commas]
Event(s) – All events	[Insert all event preferred terms separated by commas]

The information will be provided to regulatory authorities such as the Food and Drug Administration, other regulatory agencies, Organon LLC subsidiaries worldwide, and business partners with whom we have certain contractual agreements. Any information that identifies the patient directly, such as the patient's name and address, will be handled confidentially.

Enclosed is a form that Organon LLC respectfully suggests you complete and return to us at your earliest convenience. The objective is to obtain additional information to better understand the experience you reported which may improve patient safety. Your assistance in this matter is greatly appreciated. If you are located in the United States, you may provide this information by calling us at 844-674-3200, Monday- Friday 8AM to 5PM ET, or you can return the completed form via fax at 215-731-3670. If you are located outside of the United States, contact your Organon local representative office https://www.organon.com/about-organon/global-locations/ <Add Local Contact DPOC details if needed>.

The information provided concerning the reported event will be handled according to current worldwide regulatory requirements. Please read more about Organon's privacy commitment at www.Organon.com/privacy/

Sincerely,

Organon LLC Global Safety <Add Local Contact details if needed>
Phone: (+1) 844-674-3467
Fax: 215-731-3670

ORGANON **FOSAMAX/FOSAVANCE AND REPORT OF FRACTURE**

OARS #: [case_num]

REPORTER INFORMATION:

Name and title: _____

Affiliation: _____

Address: _____

_____

Daytime Telephone Number: _____ Signature and date: _____

PATIENT INFORMATION:

Patient Name / Initial	
Age	
DOB	
Gender	
Nationality / Race	

Fracture Details (check all that apply)	
Fracture location:	
Femur: ☐Proximal (☐Neck ☐Neck ☐Intertrochanteric ☐Trochanteric) ☐Shaft (☐Distal ☐Midshaft (all subtrochanteric) ☐Periprosthetic **Other long bones:** ☐Tibia (Periprosthetic? ☐Yes ☐No ☐Unknown) ☐Fibula ☐Humerus (Periprosthetic? ☐Yes ☐No ☐Unknown) ☐Ulna ☐Radius ☐Metacarpals ☐Metatarsals ☐Phalanges **Other location/bone (specify):** _____	
Diagnostic imaging used to confirm fracture:	
☐X-ray ☐CT scan ☐MRI	**Date of imaging (DD-MMM-YYYY):** _____
Major Features	
Was the fracture associated with minimal trauma or no trauma? ☐Yes ☐No (associated with significant trauma) ☐Unknown	

ORGANON **FOSAMAX/FOSAVANCE AND REPORT OF FRACTURE**

OARS #: [case_num]

Does the fracture originate at the lateral cortex and have a transverse or oblique configuration?

☐Yes

☐No (other configuration)

☐Unknown

Is the fracture:	**If complete:**
☐Complete	Does the fracture extend to through both cortices?
☐Incomplete	☐Yes ☐No ☐Unknown
☐Unknown	Is the fracture associated with a medial spike?
	☐Yes ☐No ☐Unknown
	If incomplete:
	Does the fracture involve the lateral cortex?
	☐Yes ☐No ☐Unknown

Is the fracture non-comminuted or minimally comminuted?

☐Yes

☐No (fracture is comminuted)

Is there localized periosteal or endosteal thickening of the lateral cortex at the fracture site?

☐Yes ☐No ☐Unknown

Minor features

Is there generalized increase in cortical thickness of the bone?

☐Yes ☐No ☐Unknown

Did the patient experience pain or other symptoms in the area prior to the fracture?

☐Yes, clarify: _____ ☐No ☐Unknown

Were there bilateral (same contralateral bone) incomplete or complete fractures?

☐Yes ☐No ☐Unknown

Was there a delayed healing fracture?

☐Yes ☐No ☐Unknown

Fracture treatment

☐Non-surgical reduction ☐Casting

☐Surgery ☐Revision surgery (second surgery)

☐Unknown ☐Other, specify: _____

Medical History/Risk factors (check all that apply)

Prior osteoporosis treatment

☐Estrogen

☐Selective estrogen receptor modulator (SERM)

☐Parathyroid hormone

☐Bisphosphonate:

☐Intravenous ☐Oral

How long has therapy been received? (months, years):

_____

Is there a previous or concurrent history of cancer?

☐Yes ☐No ☐Unknown

If yes, is there evidence of metastases?

☐Yes ☐No ☐Unknown

If yes, did metastases involve bones?

☐Yes ☐No ☐Unknown

Has the patient received any of the following treatments/medications?

☐Glucocorticoids (e.g., prednisone, hydrocortisone, dexamethasone, etc.)

☐Proton pump inhibitors (e.g., omeprazole, rabeprazole, etc.)

☐Thiazolidinediones (e.g., pioglitazone, rosiglitazone, etc.)

☐Anticonvulsants (e.g., phenytoin, carbamazepine, etc.)

☐Cancer therapy (e.g., chemotherapy, radiation)

If yes, which one and for how long (months, years): _____

Are there any relevant comorbid conditions?

☐Vitamin D deficiency

☐Rheumatoid arthritis

☐Metabolic bone disease (e.g., osteogenesis imperfecta, Paget's disease, hypophosphatasia)

☐Other autoimmune disorders, specify: _____

☐Smoking history. If yes, for how long: _____

☐Other, specify: _____

☐None

☐Unknown

Is there a family history of fracture, osteoporosis, or some other fragile bone disease?

☐Yes, specify: _____ ☐No

☐Unknown

Laboratory information (if available)

Were there any abnormal lab tests? ☐No ☐Unknown ☐Yes, if yes, please provide below:

Serum PTH: _____ Serum Ca: _____ 25(OH)D: _____

Alk Phos: _____ BSAP: _____ NTx: _____

CTx: _____ Phos: _____ Mg: _____

ANNEX 6 – DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

There are no additional risk minimization activities for alendronic acid / colecalciferol.