PART VI SUMMARY OF THE RISK MANAGEMENT PLAN (by medicinal product)

Format and content of the summary of the RMP

The summary of the RMP part VI contains information based on RMP modules SI, SVIII and RMP parts IV and V. Summary of risk management plan is applicable for all products: alendronic acid, alendronic acid with alfacalcidol and alendronic acid/colecalciferol, since safety concerns are related to the active substance - alendronic acid.

Routine risk minimisation activites are considred sufficient for each safety concern.

Please refer to item VI.3 below for 'Summary of safety concerns' and item VI.4 for 'Summary of risk minimisation activities by safety concern' for each medicinal product.

VI.1. Overview of disease epidemiology

Due to its important prevalence worldwide, **osteoporosis** in post-menopausal women and in men is considered as a serious public health concern. Currently it is estimated that over 200 million people worldwide suffer from this disease. Approximately 30% of all postmenopausal women have osteoporosis in the United States and in Europe. At least 40% of these women and 15-30% of men will sustain one or more fragility fractures in their remaining lifetime. Ageing of populations worldwide will be responsible for a major increase of the incidence of osteoporosis in postmenopausal women. It has been shown that an initial fracture is a major risk factor for a new fracture.

VI.2. Summary of existing efficacy data

The applications concern active substances which have been in clinical use for long time. Alendronic acid alone or in combinations with vitamin D is effective therapy in the treatment of osteoporosis.

In addition, the use of a fixed combination tablet instead of the individual administration of the two compounds is expected to be more convenient to patients (and thus to improve compliance) by limiting the number of tablets they need to take.

VI.3. Summary of safety concerns

Important identified risks	What is known	Preventability
Osteonecrosis of the jaw (ONJ)	Osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection (including osteomyelitis), has been reported in patients with cancer receiving treatment regimens including primarily intravenously administered bisphosphonates. Many of these patients were also receiving chemotherapy and corticosteroids. Osteonecrosis of the jaw has also been reported in patients with osteoporosis receiving oral bisphosphonates. While on treatment, the patients with poor dental status should avoid invasive dental procedures if possible. For patients who develop osteonecrosis of the jaw while on bisphosphonates therapy, dental surgery may exacerbate the condition.	Prescribers should ensure that patients with cancer go to their dentist for a check-up and find out if they need any dental treatment before they start taking a bisphosphonate. They should also ensure that patients who do not have cancer go to their dentist for a check-up if their dental health is poor. During treatment with bisphosphonates, patients should maintain good oral hygiene, go for routine dental check-ups and report any symptoms in the mouth such as loose teeth, pain or swelling. Dentists should be aware of the risks in patients taking bisphosphonates and should keep dental treatment as conservative and preservative as possible. Reducing the bisphosphonate dose, duration of therapy and frequency of administration may reduce the risk of ONJ while maintaining the therapeutic benefits of these drugs.
Hypocalcaemia	Due to the positive effects of alendronate in increasing bone mineral, decreases in serum calcium and phosphate may occur especially in patients taking glucocorticoids in whom calcium absorption may be decreased. These are usually small and asymptomatic. However, there have been rare reports of symptomatic hypocalcaemia, which occasionally have been severe and often occurred in patients with predisposing conditions (e.g. hypoparathyroidism, vitamin D deficiency and calcium malabsorption).	Hypocalcaemia must be corrected before initiating therapy with alendronate. Other disturbances of mineral metabolism (such as vitamin D deficiency and hypoparathyroidism) should also be effectively treated. In patients with these conditions, serum calcium and symptoms of hypocalcaemia should be monitored during therapy with alendronate. Hypocalcaemia can be avoided or attenuated by the administration of adequate vitamin D and calcium supplements, starting about two weeks before the administration of the bisphosphonate. Drug must not be used in patients with hypocalcaemia.
Oesophageal adverse effects	Oesophageal reactions (sometimes severe and requiring hospitalisation), such as oesophagitis, oesophageal ulcers and oesophageal erosions, rarely followed by oesophageal stricture, have been reported in patients receiving alendronate. The risk of severe oesophageal adverse experiences appears to be greater in patients who fail to take alendronate properly and/or who continue to take alendronate after developing symptoms suggestive of oesophageal irritation.	Physicians should be alert to any signs or symptoms signalling a possible oesophageal reaction and patients should be instructed to discontinue alendronate and seek medical attention if they develop symptoms of oesophageal irritation such as dysphagia, pain on swallowing or retrosternal pain, new or worsening heartburn. It is very important that the full dosing instructions are provided to, and understood by the patient. Patients should be informed that failure to follow these instructions may increase their risk of oesophageal problems.

Important identified risks	What is known	Preventability
		Drug must be used according to the instructions. Patients should not chew the tablet or allow it to dissolve in their mouth, as there is a risk that oropharyngeal ulcers may develop. In addition, the drug must not be used in patients with abnormalities of the oesophagus and other factors which delay oesophageal emptying such as stricture or achalasia.

Important potential risks	What is known
Atypical femoral fracture	Atypical subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonate therapy (drug class effect), primarily in patients receiving long-term treatment for osteoporosis. These fractures occur after minimal or no trauma and some patients experience thigh or groin pain, often associated with imaging features of stress fractures, weeks to months before presenting with a completed femoral fracture. Fractures are often bilateral; therefore the contralateral femur should be examined in bisphosphonate-treated patients who have sustained a femoral shaft fracture. Poor healing of these fractures has also been reported. Discontinuation of bisphosphonate therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient, based on an individual benefit risk assessment. During bisphosphonate treatment patients should be advised to report any thigh, hip or groin pain and any patient presenting with such symptoms should be evaluated for an incomplete femur fracture.
Atrial fibrillation	Atrial fibrillation has been reported with some bisphosphonates (drug class effect). The potential of developing atrial fibrillation with alendronic acid is not known.
Hypersensitivity reactions	Drug is contraindicated in patients with known hypersensitivity to active substances or to any of the excipients. The following adverse reactions have been reported: hypersensitivity reactions including urticaria and angioedema
Ocular advesre events	There have been reports of eye inflammation (uveitis, scleritis, episcleritis).

Important missing information	What is known
Use during pregnancy and lactation	Products containing alendronic acid should not be used during pregnancy and lactation. Overdosage with vitamin D derivatives should be avoided during pregnancy, as persistent hypercalcaemia in the infant can induce physical and mental retardation, supravalvular aortic stenosis and retinopathy.
Use in patients below 18 years of age	Products containing alendronic acid should not be used in children and adolescents.

VI.4. Summary of risk minimisation activities by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Osteonecrosis of the jaw (ONJ)	Labelling: Risk has been highlighted in the SmPC in section 4.4 *Special warnings and special precautions for use*, and in section 4.8 *Undesirable effects*. Prescription-only medicine	None
Hypocalcaemia	Labelling: Risk has been highlighted in the SmPC in sections 4.3 *Contraindications*, 4.4 *Special warnings and precautions for use, 4.8 Undesirable effects* and 4.9 *Overdose*. Prescription-only medicine	None
Oesophageal adverse effects (oral formulations)	Labelling: Risk has been highlighted in the SmPC in section 4.3 *Contraindications,* 4.4 *Special warnings and precautions for use*, 4.8 *Undesirable effects* and in section 4.9 *Overdose*. Prescription-only medicine	None
Atypical femoral fractures	Labelling: [Section 4.2 *Posology and method of administration*] includes information about the need to periodically evaluate the need for continuing bisphosphonate treatment, particularly after 5 years of treatment, on an individual patient basis. Warning [Section 4.4 *Special warnings and special precautions for use*] on the risk of atypical fractures of the femur and listed as a class adverse reaction in [Section 4.8 *Undesirable effects*] SmPC. Prescription-only medicine	None
Atrial fibrillation	Routine pharmacovigilance will be sufficient to identify risk with alendronic acid and its combinational products with vit. D. Prescription-only medicine	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Hypersensitivity reactions	Labelling: Risk has been highlighted in the SmPC in sections 4.3 *Contraindications* and 4.8 *Undesirable effects*. Prescription-only medicine	None
Ocular adverse events	Labelling: Risk has been highlighted in the SmPC in section 4.8 *Undesirable effects*. Prescription-only medicine	None
Use during pregnancy and lactation	Labelling: Information is given in section 4.6 *Fertility, pregnancy and lactation*; alendronic acid and its combinational products with vitamin D, should not be used during pregnancy and lactation. Prescription-only medicine	None
Use in patients below 18 years of age	Labelling: Information is given in section 4.2 Alendronic acid and alendronic acid/colecalciferol are not recommended for use in children under the age of 18 years due to insufficient data on safety and efficacy in conditions associated with paediatric osteoporosis. Additionally for alendronic acid with alfacalcidol Drug is contraindicated in children and adolescents. Contraindication is also stated in section 4.3. Prescription-only medicine	None

VI.5. Planned post-authorisation development plan

Not applicable.

VI.6. Summary of changes to the risk management plan over time

Version	Reason for change	Change type	Sections
version 1.0, 21 February 2012 for Bisphosphonates	Version 1.0 was EU-RMP for all bisphosphonates (INN: alendronic acid, clodronic acid, pamidronic acid, risedronic acid). Based on the regulatory authorities' request, the first RMP for alendronic acid, alendronic acid/colecalciferol and alendronic acid/alfacalcidol was prepared (version 1.0 released on 06 August 2012).	Formal change.	Scope, title
version 1.0, 06 August 2012 for Alendronic acid/ Alendronic acid/colecalciferol and Alendronic acid/alfacalcidol	Version was upgraded to version 2 to emphasise that EU-RMP for alendronate and combination was continuation of EU-RMP for all bisphosphonates	Formal change.	Version change on title page and header
version 2.0, 06 August 2012 for Alendronic acid/ Alendronic acid/colecalciferol and Alendronic acid/alfacalcidol	Clinical efficacy study on alendronic acid/colecalciferol has been finished	The data in regard to clinical efficacy study on alendronic acid/colecalciferol was included. RMP was also aligned with the newly proposed EU-RMP template.	All sections have been re-organized and/or updated as compared to version 2.0 based on GVP template. Part II Module SIII Clinical Trial Exposure and Part VII Annexes 3 and 4 were updated.