Summary of the risk management plan by product

1 Elements for summary tables in the EPAR

1.1 Summary table of Safety concerns

Summary of safety concerns	
Important identified risks	• Osteonecrosis of the jaw • Local irritation of the upper gastro-intestinal mucosa • Oesophageal reactions (such as oesophagitis, oesophageal ulcers and oesophageal erosions, oesophageal stricture)
Important potential risks	• Atypical femoral fractures
Missing information	• Use in Pregnant women • Use in patients below 18 years of age

1.2 Table of ongoing and planned studies in the post-authorisation Pharmacovigilance Development Plan

Not applicable

1.3 Summary of the Post -authorisation efficacy development plan

Not applicable

1.4 Summary table of risk minimisation measures

Safety Concern	**Routine Risk Minimisation measures**	**Additional Risk Minimisation measures**
Osteonecrosis of the jaw	• Mentioned in special warning and precaution for use section 4.4 of SmPC • Listed in section 4.8 of SmPC • Mentioned in package leaflet. • Prescription only medicine.	Not applicable
Local irritation of the upper gastro-intestinal mucosa	• Mentioned in section 4.2 of SmPC • Mentioned in special warning and precaution for use section 4.4 of	Not applicable

	SmPC. • Listed in section 4.8 • Mentioned in package leaflet. • Prescription only medicine.	
Oesophageal reactions (such as oesophagitis, oesophageal ulcers and oesophageal erosions, oesophageal stricture)	• Mentioned in special warning and precaution for use section 4.4 of SmPC. • Listed in section 4.8 of SmPC • Mentioned in package leaflet. • Prescription only medicine.	Not applicable
Atypical femoral fractures	• Mentioned in special warning and precaution for use section 4.4 of SmPC • Listed in section 4.8 of SmPC • Mentioned in package leaflet. • Prescription only medicine.	Not applicable
Use in Pregnant women	• Mentioned in section 4.6 of SmPC • Mentioned in package leaflet. • Prescription only medicine.	Not applicable
Use in patients below 18 years of age	• Mentioned in Posology and method of administration in section 4.2 of the SmPC. • Mentioned in package leaflet. • Prescription only medicine.	Not applicable

2 Elements for a public summary

2.1 Overview of disease epidemiology (for each indication)

Indication/target population	**Postmenopausal Osteoporosis**
Incidence and prevalence	The incidence of osteoporosis in postmenopausal women continues to increase with progressively aging populations. Currently, it is estimated that over 200 million people worldwide have osteoporosis. The incidence of hip fracture in women aged 50 years or above was calculated and expressed as the annual number of hip fractures per 10,000 women. In the United States and the European Union, about 30% of all postmenopausal women have osteoporosis, and it has been predicted that more than 40% of them will suffer one or more fragility fractures during their remaining lifetime. One out of three postmenopausal women and one out of five men over the age of 50 years will experience osteoporotic fractures.
Demographics of the target population – age, sex, race/ethnic origin	The prevalence of osteoporosis increased with age. Significantly higher among women than among men. It was found that Whites are having more frequencies to get post-menopausal osteoporosis compared followed by Blacks and Hispanics.
Risk factors for the disease	Early menopause, a maternal history of hip fracture, a fracture after 40 years of age, low body weight, or specific diseases and treatments increase susceptibility to fractures Postmenopausal women are at the greatest risk of developing osteoporosis because of the accelerated loss in bone mass associated with menopause, include advanced age, genetics, lifestyle factors (such as low calcium and vitamin D intake, smoking), thinness, and menopause status.
Main treatment options	Pharmacological management is the primary prevention of osteoporotic fractures in patients at high risk or secondary prevention in patients who have already sustained a fracture. Management focuses first on non-pharmacologic measures, such as a balanced diet, adequate calcium and vitamin D intake, adequate exercise, smoking cessation, avoidance of excessive alcohol intake, and fall prevention.

	Calcium is a key element in the therapy of osteoporosis. Adequate calcium intake throughout life is essential for optimizing peak bone mass and may affect the rate at which bone is lost later in life. Calcium alone is inadequate to completely inhibit the rapid bone loss that occurs at menopause but is necessary to optimize response to antiresorptive agents. (Calcium carbonate and tribasic calcium phosphate have the greatest percentage of elemental calcium). The two exogenous sources of vitamin D are ergosterol (vitamin D2) from plant sources and cholecalciferol (vitamin D3) from animal sources, such as fish liver oils and fortified milk, presence enhances GI absorption of calcium. Postmenopausal estrogen therapy, taken with or without progestin. And bisphosphonates are compounds that adsorb onto hydroxyapatite crystals. Alendronate is approved by the FDA for the prevention of osteoporosis in postmenopausal women.
Mortality and morbidity (natural history)	Hip fractures are the most serious, since 10–20% more women die than expected for age within the first year, and the excess mortality is even greater for men. The risk of death is greatest immediately after the fracture and decreases over time. Excess morbidity and mortality caused by osteoporosis-related fractures.

2.2 Summary of treatment benefits

As per the evidence-based position statement published by The North American Menopause Society (NAMS) in 2006 recommendations for the prevention/management/treatment of osteoporosis in postmenopausal women as follows:

Lifestyle approaches to prevent bone loss and fractures;

- Nutrition, including adequate intakes of calcium, vitamin D, vitamin K, magnesium, protein, and isoflavones
- Exercise
- Fall prevention
- Smoking cessation
- Alcohol avoidance

Pharmacologic approaches for the prevention and/or treatment of osteoporosis;

- Estrogen or estrogen plus progestin therapy

- Bisphosphonates (alendronate, risedronate, ibandronate, zoledronic acid, etidronate)
- Selective estrogen-receptor modulators, such as raloxifene
- Parathyroid hormone 1-34 (teriparatide)
- Calcitonin
- Combination therapies (considered, but no recommendation made for or against)
- Tibolone (not approved in the United States or Canada for osteoporosis prevention)
- New/experimental therapies: strontium ranelate, parathyroid I-84, bazedoxifene, lasofoxifene, denosumab (considered, but no definitive recommendation made)

Bisphosphonates are the first-line drugs for treating postmenopausal women with osteoporosis. They have reduced the risk of vertebral fractures by 40% to 70% and reduced the incidence of nonvertebral fracture, including hip fracture, by about half this amount.

Alendronate is comes under the group of bisphosphonates. In osteoporosis the strength of the bones is reduced and this can increase the chances of getting bone fractures. Alendronate can make bones stronger in people with osteoporosis which can reduce the chances of getting bone fractures.[11]

2.3 Unknowns relating to treatment benefits

None identified.

2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Bone damage in the jaw (osteonecrosis of the jaw)	Osteonecrosis of the jaw generally associated with tooth extraction and/or local infection (including osteomyelitis) has been reported in patients with cancer 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	Yes, • The following risk factors should be considered when evaluating an individual's risk of developing osteonecrosis of the jaw: - potency of the bisphosphonate (highest for zoledronic acid), route of administration (see above) and cumulative dose - cancer, chemotherapy, radiotherapy, corticosteroids, smoking - a history of dental disease, poor oral hygiene, periodontal disease, invasive dental procedures and poorly fitting dentures

Risk	What is known	Preventability
		• A dental examination with appropriate preventive dentistry should be considered prior to treatment with oral bisphosphonates in patients with poor dental status. • While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop osteonecrosis of the jaw while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of the jaw. • Clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment. • During bisphosphonate treatment, all patients should be encouraged to maintain good oral hygiene, receive routine dental check-ups, and report any oral symptoms such as dental mobility, pain, or swelling.
Local irritation of the upper gastro-intestinal mucosa	Alendronate can cause local irritation of the upper gastro-intestinal lining (mucosa). Because there is a potential for worsening of the underlying disease, caution should be used when alendronate is given to patients with active upper gastro-intestinal problems, such as difficulty swallowing (dysphagia), oesophageal disease, gastritis, inflammation of the first part of the small intestine (duodenitis), ulcers, or with a recent history (within the previous year) of	Yes, - Instructions given in section 4.2 Posology and method of administration of SmPC - Contraindicated in abnormalities of the oesophagus and other factors which delay oesophageal emptying such as stricture or achalasia (a condition which impairs the ability of the oesophageal smooth muscle to

Risk	What is known	Preventability
	major gastro-intestinal disease such as peptic ulcer, or active gastro-intestinal bleeding, or surgery of the upper gastro-intestinal tract other than pyloroplasty (a surgical procedure to widen the opening of the lower portion of the stomach which connect to the duodenum).	move food effectively to the stomach). - 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.
The tube that connects your mouth with your stomach damages/injury (Oesophageal reaction)	Oesophageal reactions (sometimes severe and requiring hospitalisation), such as oesophagitis, oesophageal ulcers and oesophageal erosions, rarely followed by oesophageal stricture, have been reported in patients receiving alendronate. Physicians should therefore be alert to any signs or symptoms signaling 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 central chest (retrosternal) pain, new or worsening heartburn. 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. In patients with known Barrett's oesophagus, prescribers should consider the benefits and potential risks of alendronate on an individual patient basis.	Yes, - Instructions given in section 4.2 Posology and method of administration - 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 potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Bone fracture (Atypical femoral fractures)	Atypical femoral fractures have been reported with bisphosphonate therapy, 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. Fracture often occur on both sides ; therefore the opposite 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. As per the CMDh ‘atypical femoral fracture’ as a potential risk following the commission decision on the Article 31 of Directive 2001/83/EC referral concerning bisphosphonates.

Missing information

Risk	What is known
Use in pregnant woman	• There are insufficient data regarding the use of alendronate in pregnant women. Animal studies showed that effects on foetal bone formation at high doses. Alendronate given to pregnant rats caused obstruction of labour related to low blood calcium levels.
Use in patients below 18 years of age	• Alendronate sodium is 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

2.5 Summary of additional risk minimisation measures by safety concern

Alendronate has 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. The measures in these documents are known as routine risk minimisation measures.

Alendronate has no additional risk minimisation measures.

2.6 Planned post authorisation development plan

Not applicable

2.7 Summary of changes to the risk management plan over time

Major changes to the risk management plan over time

Version	Date	Safety Concerns	Comment
Not applicable	Not applicable	Not applicable	Not applicable