VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Osteoporosis is a disease in which the density and quality of bone are reduced. Bones become more porous and fragile and therefore the risk of fracture is significantly increased. The loss of bone occurs progressively and very often there are no symptoms until the first fracture occurs. In the United States, Europe and Japan, osteoporosis affects about 75 million people. Using the World Health Organisation (WHO) criteria, 30% of postmenopausal Caucasian women have osteoporosis at the hip, lumbar spine or distal forearm. This is comparable with the risk of fracture for a 50 year old woman at one of these three sites. In comparison, the estimated lifetime fracture risk for Caucasian men is 13 to 21%. By the age of 80 years, 70% of women are osteoporotic at the hip, lumbar spine or distal forearm. Therefore, ageing of populations worldwide may be responsible for a major increase of the incidence of osteoporosis in postmenopausal women.

VI.2.2 Summary of treatment benefits

Bisphosphonates such as alendronate are first-line therapies for the prevention of fracture in high-risk individuals. The role of alendronate has subsequently been underscored by a range of studies extending the clinical indications for its use and consolidating the effect on reducing both vertebral and non-vertebral fracture risk.
Adequate calcium and vitamin D are important for maintaining bone health and for the effectiveness of anti-resorptive therapy. Therefore the fixed combination tablet of alendronate and Cholecalciferol, especially in the older patients with osteoporosis, may be more suitable for them because the number of tablets for the osteoporosis they need to take is limited

VI.2.3 Unknowns relating to treatment benefits

There are no or limited amount of data from the use of alendronate in pregnant women.

The safety and efficacy of the medicinal product in children less than 18 years of age have not been established.

There is lack of experience of [Alendronate/Cholecalciferol] use in patients with renal impairment where creatinine clearance is less than 35 ml/min

VI.2.4 Summary of safety concerns

Important identified risks		
Risk	**What is known**	**Preventability**
Safety concern in lay language ***(medical term)***	**Brief summary in lay language**	**Whether risk can be minimised or mitigated, and how**
Bone damage in the jaw *(Osteonecrosis of the jaw)*	Osteonecrosis of the jaw (ONJ) is a severe bone disease that affects the jaws. It is a condition found in patients who have received intravenous and oral forms of bisphosphonate therapy for various bone-related conditions. Osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection (including osteomyelitis), has been reported in patients with cancer and in patients with osteoporosis receiving oral bisphosphonates. Severe cases of osteonecrosis of the jaw may require surgical removal of the affected bone.	There are many factors that should be considered to minimise osteonecrosis of the jaw occurrence in a patient. Cancer, chemotherapy, radiotherapy, corticosteroids, smoking are factors to be take in consideration. In addition, history of dental disease, poor oral hygiene, periodontal disease, invasive dental procedures and poorly fitting dentures. Therefore, 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. However, for patients who develop osteonecrosis of the jaw while on bisphosphonate

		therapy, dental surgery may exacerbate the condition. 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.
Undesirable effects in the tube connecting mouth with stomach *(Oesophageal adverse events)*	Oesophageal reactions such as oesophagitis, oesophageal ulcers and oesophageal erosions, rarely followed by oesophageal stricture, have been reported in patients receiving alendronate. Sometimes these reactions are severe and require hospitalisation. The risk of severe oesophageal adverse reactions appears to be greater in patients who fail to take alendronate properly and/or who continue to take alendronate after developing symptoms suggestive of oesophageal irritation.	Physicians should to be alert to any signs or symptoms signalling a possible oesophageal reaction and patients should be instructed to discontinue alendronate and seek medical attention if they develop symptoms of oesophageal irritation such as dysphagia, pain on swallowing or retrosternal pain or new or worsening heartburn. Alendronate can cause local irritation of the upper gastrointestinal mucosa. Because there is a potential for worsening of the underlying disease, caution should be used when alendronate is given to patients with active upper gastrointestinal problems, such as dysphagia, oesophageal disease, gastritis, duodenitis, ulcers, or with a recent history (within the previous year) of major gastrointestinal disease such as peptic ulcer, or active gastrointestinal bleeding, or surgery of the upper gastrointestinal tract other than pyloroplasty In patients with known Barrett's oesophagus, prescribers should consider the

		benefits and potential risks of alendronate on an individual patient basis. *It is very important that patients follows instructions for drug administration*

Important potential risks	
Risk	**What is known (Including reason why it is considered a potential risk)**
Atypical femoral fractures	Atypical subtrochanteric and diaphyseal 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. 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.

Missing information	
Risk	**What is known**
Use during pregnancy and lactation	*Pregnancy* There are no or limited amount of data from the use of alendronate in pregnant women. Studies in animals have shown reproductive toxicity. Alendronate given during pregnancy in rats caused dystocia related to hypocalcaemia. Studies in animals have shown hypercalcaemia and reproductive toxicity with high doses of vitamin D. *Breastfeeding* It is unknown whether alendronate/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. Alendronate should not be used during breast-feeding. Cholecalciferol and some of its active metabolites pass into breast milk.

	Therefore products containing alendronate should not be used during pregnancy and lactation
Use in patients below 18 years of age	The safety and efficacy of the medicinal product in children less than 18 years of age have not been established. Therefore, it should not be used in children less than 18 years of age because no data are available for the alendronic acid/cholecalciferol combination. Products containing alendronic acid should not be used in children and adolescents because of the small number of patients with osteogenesis imperfecta under the age of 18 years been studied.
Use in patients with severe renal insufficiency [GFR less than 35 mL/min]	Preclinical studies show that alendronate that is not deposited in bone is rapidly excreted in the urine. No evidence of saturation of bone uptake was found after chronic dosing with cumulative intravenous doses up to 35 mg/kg in animals. Although no clinical information is available, it is likely that, as in animals, elimination of alendronate via the kidney will be reduced in patients with impaired renal function. Therefore, somewhat greater accumulation of alendronate in bone might be expected in patients with impaired renal function [Invented name] is not recommended for patients with renal impairment where creatinine clearance 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.

VI.2.5 Summary of risk minimisation measures 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.

•

VI.2.6 Planned post authorisation development plan

Not applicable

VI.2.7 Summary of changes to the risk management plan over time

Version	Date	Safety concerns	Change

1.0	06.08.2015	**Important identified risks** • Osteonecrosis of the jaw • Hypocalcaemia • Oesophageal adverse events **Important potential risks** • Atypical femoral fractures • Hypersensitivity reactions **Missing information** • Use during pregnancy and lactation • Use in patients below 18 years of age	Initial version
1.0	05.12.2016	**Important identified risks** • Osteonecrosis of the jaw • Oesophageal adverse events **Important potential risks** • Atypical femoral fractures **Missing information** • 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]	Implementation of day70 and day 100 assessor's comments
1.0	27.04.2017	**Important identified risks** • Osteonecrosis of the jaw • Oesophageal adverse events **Important potential risks** • Atypical femoral fractures **Missing information** • 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]	Implementation of day 203 assessor's comments to remove PRC reference from RMP acceptable version ALENDRO-CHOLECA-v1-051216