VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Postmenopausal osteoporosis [1, 2, 3]

"Osteoporosis is a disease in which the density and quality of bone are reduced. As the bones become more porous and fragile, the risk of fracture is significantly increased. Bone loss occurs progressively and very often there are no symptoms until the first fracture occurs. Osteoporosis is estimated to affect about 75 million people across Europe, USA and Japan and occurs more frequently in women than in men. The risk for osteoporosis increases with age, especially in postmenopausal women."

VI.2.2 Summary of treatment benefits

Postmenopausal osteoporosis and Vitamine D deficiency

Alendronic acid/Cholecalciferol studies

The benefic effect of the Alendronic acid/Cholecalciferol combination (alendronate 70 mg/vitamin D_3 2800 IU) on vitamin D blood concentration was demonstrated in a multinational study involving post-menopausal women affected by osteoporosis. Patients were divided in two groups received respectively 70 mg/2800 IU of Alendronic acid/Cholecalciferol or alendronate 70 mg once a week for 15 weeks. In the group taking Alendronic acid/Cholecalciferol the percentage of patients with vitamin D insufficiency were reduced by 62.5 while the percentage of the ones with vitamin D deficiency was reduced by 92% compared to the group taking alendronate only.

Another study demonstrated that the alendronate 70 mg/vitamin D3 5600 IU strength once a week was more effective in reducing vitamin D deficiency than the 70 mg/2800 IU.

Alendronate studies

The efficacy of alendronate on increasing bone mass and reducing the number of fracture episodes over time in post-menopausal women was demonstrated in different studies.

Two studies displayed that subjects treated with alendronate 10 mg/day had an increased bone mineral density (BMD) (i.e. a major concentration of calcium and other types of minerals in the bones) after three years compared to subjects treated only with placebo (i.e. an inactive substance). There was also a 48 % reduction in the incidence of one or more vertebral fractures in the alendronate group compared to the placebo group.

Two further studies showed that alendronate is also more effective than placebo in reducing further fractures in osteoporotic women with a history vertebral fractures and of hip fractures.

VI.2.3 Unknowns relating to treatment benefits

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[1] Monique Bethel, MD - Osteoporosis Treatment & Management. Available at: http://emedicine.medscape.com/article/330598. Accessed on 07/08/2015.

[2] Cleveland Clinic - Menopause&Osteoporosis. Available at http://my.clevelandclinic.org/health/diseases_conditions/hic-what-is-perimenopause-menopause-postmenopause/hic_Menopause_and_Osteoporosis. Accessed on 07/08/2015.

[3] EFFO and NOF (1997) Who are candidates for prevention and treatment for osteoporosis? Osteoporos Int 7:1

Use in patients below 18 years of age

The safety and efficacy of alendronic acid/cholecalciferol combination in children less than 18 years of age have not been established, this combination should not be used in this population.

Use in patients severe renal insufficiency (with creatinine clearance lower than 35 ml/min)

Alendronate/cholecalciferol combination is not recommended for patients with renal impairment where creatinine clearance is less than 35 ml/min, due to lack of experience. There are no recommended doses for these patients.

Use during pregnancy and lactation

There are no or limited amount of data from the use of alendronate in pregnant women. Studies in animals have shown reproductive toxicity.

It is unknown whether alendronate or its metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. Cholecalciferol and some of its active metabolites pass into breast milk. Thus alendronate/cholecalciferol combination should not be used during breast-feeding.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Side effects involving the foodpipe (Oesophageal adverse experiences)	There is a risk of oesophageal irritation and ulcer together with a series of related upper gastrointestinal adverse reactions, such as upset stomach, heartburn, gastritis.	Yes, following the instructions provided in the SmPC and PIL amongst which: • Swallowing the drug after getting up for the day with a full glass of water (not less than 200 ml) • Swallowing the whole tablet without crushing it • Not lying down until after the first food of the day and for at least 30 minutes after taking the drug • Not taking the drug at bedtime or before arising for the day.
Death of the jaw bone tissue (Osteonecrosis of the jaw)	Osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection, has been reported in patients affected by cancer (many of them concomintantly receiving cancer therapies such as chemotherapy or anti-	Yes, following the instructions provided in the SmPC and PIL amongst which: • Undergoing a dental examination with

Risk	What is known	Preventability
	inflammatory drugs such as corticosteroids) or affected by osteoporosis (a disease ususally silent that cause a progressive loss of bone mass) who are receiving bisphosphonates. Some risk factors can increase the probability of experiencing osteonecrosis are: • potency of the bisphosphonate, route of administration and total dose administered • concomitant cancer and cancer therapies such as chemotherapy and/or radiotherapy • corticosteroids (a group of anti-inflammatory drugs), smoking • a history of dental disease and/or poor oral hygiene	appropriate preventive dentistry prior to treatment with oral bisphosphonates in patients with poor dental status • While on treatment, if possible, avoiding invasive dental procedures such as surgery if possible • Avoiding smoking • Using bisphosphonates with low potency and/ or lowering the dose administered if possible • Encouraging patients during bisphosphonate treatment, to maintain good oral hygiene, receive routine dental check-ups, and report any oral symptoms such as dental mobility, pain or swelling.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Unusual form fracture involving the strongest part of the thigh bone by features distinctly different from 'typical' osteoporotic thigh bone fracture (Atypical femoral fracture)	Some patients receiving long-term bisphosphonates treatment for osteoporosis experienced unsual form (transverse or short oblique) fracture involving the strongest part of the bone primarily in patients. These poor healing fractures often affecting both the legs occurred after minimal or no trauma and some patients experienced thigh or groin pain, often associated with imaging features of fractures, weeks to months before presenting with a completed femoral fracture.

Missing information

Risk	What is known
Use in pregnant and breastfeeding women (Use during pregnancy and lactation)	There are no or limited data from the use of alendronate + cholecalciferol combination in pregnant and breastfeeding women, thus should not be used. There are no or limited amount of data from the use of alendronate

Risk	What is known
	in pregnant women. Studies with alendronate in rats have shown reproductive (skeletal) toxicity. Studies in animals with high doses of vitamin D have shown hypercalcaemia (high calcium blood concentration) and reproductive toxicity. It is unknown whether alendronate or its metabolites are excreted in human milk. Cholecalciferol and some of its active metabolites pass into breast milk. The potential risk for newborns/infants is unknown.
Use in children and adolescents (Use in patients below 18 years of age)	The safety and efficacy of alendronate + cholecalciferol combination in children and adolescent less than 18 years of age have not been established (no data are available) thus should not be used in this population.
Use in patient with severe renal impairment and whose creatinine filtration, an indicator of kidney function, is lower than 35 mL/min (Use in patients with severe renal insufficiency [GFR less than 35 mL/min])	Alendronate + cholecalciferol combination is not recommended for patients with severe renal impairment when creatinine clearance is less than 35 ml/min, due to lack of experience in this population.

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.

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	Comment
1.0	11/08/2015	**Important identified risks:** • Oesophagitis, oesophageal ulcer • Hypocalcaemia • Osteonecrosis of the jaw **Important potential risks:** • Atypical fractures of the femur **Important missing information:** • Use during pregnancy and	Initial version.

Version	Date	Safety Concerns	Comment
		lactation • Use in patients below 18 years of age • Use in patients with creatinine clearance lower than 35 ml/min • Effects on fertility	
1.1	01/12/2016	**Important identified risks:** • Oesophageal adverse experiences • Osteonecrosis of the jaw **Important potential risks:** • Atypical femoral fracture **Important 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]	The RMP was amended according to Dutch NCA acting as RMS request to update RMP safety specification in line with the originator's one and to implement additional risk minimization measures concerning the risk of osteonecrosis of the jaw in the form of educational materials for patients (patient reminder card) in line with PRAC's decision (13 March 2015, EMA/169618/2015) for Aclasta and other bisphosphonate products.
1.2	13/04/2017	**Important identified risks:** • Oesophageal adverse experiences • Osteonecrosis of the jaw **Important potential risks:** • Atypical femoral fracture **Important 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]**	According to the Assessor evaluation, the additional Risk Minimisation Measure (Patient Cards) for the risk of Osteonecrosis of Jaw should be removed from the document, as it is applicable for parentheral formulation of bisphosphonates, not oral form.