VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Prevention of skeletal related events in adult patients with advanced malignancies involving bone:

The skeleton is commonly affected by metastatic cancer (cancer that has spread from one part of the body to the), and tumors arising from the breast, prostate, thyroid, lung, and kidney possess a special natural tendency to spread to bone. The decline in quality of life and eventual death is mainly due to skeletal complications and their subsequent treatment. Common skeletal-related

events include pathological fractures, spinal cord compression, radiation to the bone or surgery to the bone. Bone pain can result from structural damage, periosteal (a membrane that covers the outer surface of all bones, except at the joints of long bones) irritation, and nerve entrapment. Metastatic bone pain can be intermittent or constant, and people with bone metastases often report inadequate pain relief with pain killers. Hypercalcemia (Too much calcium in blood) occurs in 5-10% of all patients with advanced cancer but is most common in patients with breast carcinoma, multiple myeloma (a type of blood cancer), and squamous carcinomas of the lung (a cancer lung's skin) and other primary sites. Pathologic fractures are a relatively late complication of bone involvement. Mobility may be reduced because of bone pain and other complications.

Treatment of adult patients with tumour-induced hypercalcaemia (TIH):

Tumor-induced hypercalcemia (Too much calcium in blood) (TIH) is the second most common paraneoplastic syndrome (a set of signs and symptoms that are the consequence of cancer) with reported incidence of 5-30% amongst advanced malignancies. Multiple myeloma (a type of blood cancer), hepatoma (liver cancer), lung cancer and breast cancer were common cancers associated with TIH. It most commonly disturbs gastrointestinal (relating to the stomach and the intestines), neurological (relating to nervous system), kidney and cardiovascular (related to heart and blood vessels) functions. The early symptoms of TIH are non-specific and the diagnosis is usually suspected when patients present with neurological symptoms such as lethargy (a lack of energy and enthusiasm), drowsiness (sleepiness), disorientation, stupor (a state of near-unconsciousness) and coma. Except in patients with multiple myeloma and breast cancer, the prognosis (a forecast of the likely outcome of a situation) of the cancer patients with TIH is usually poor, with a mean survival rate of 2-3 months. Enhanced bone resorption (a process of transferring calcium from bone fluid to the blood) is the primary cause of hypercalcemia of malignancy.

VI.2.2 Summary of treatment benefits

Zoledronic acid is used to prevent bone complications, e.g. fractures, in adult patients with bone metastases (spread of cancer from primary site to the bone) and to reduce the amount of calcium in the blood in adult patients where it is too high due to the presence of a tumour.

Prevention of skeletal related events in adult patients with advanced malignancies involving bone:

In 2 studies, use of zoledronic acid 4 mg in prostate cancer or in solid tumours other than breast or prostate cancer was found to be associated with significant reduction in the proportion skeletal related events, delayed median time to first skeletal related event, and reduced the skeletal morbidity rate. In a third clinical trial, use of zoledronic acid 4 mg in patients with multiple myeloma or breast cancer with at least one bone lesion demonstrated comparable efficacy to 90 mg pamidronate in the prevention of skeletal related events. Study of Zoledronic acid 4 mg in randomized placebo controlled trial in patients with documented bone metastases from breast cancer showed low skeletal related events rate for zoledronic acid than placebo (0.628 Vs 1.096).

Treatment of adult patients with tumour-induced hypercalcaemia (TIH):

Two initial multicentre studies in patients with TIH showed faster normalisation of corrected serum calcium at day 4 with use of 8 mg zoledronic acid and at day 7 with use of 4 mg and 8 mg zoledronic acid. Median time to normocalcaemia was 4 days. In clinical trials 69 patients who relapsed or were refractory to initial treatment (zoledronic acid 4 mg, 8 mg or pamidronate 90 mg) were retreated with 8 mg zoledronic acid. The response rate in these patients was about 52%.

These studies were conducted for Zometa by Novartis Europharm Limited and no studies were conducted by Accord to evaluate the efficacy of zoledronic acid considering its similarity to the reference product.

VI.2.3 Unknowns relating to treatment benefits

Not applicable

VI.2.4 Summary of safety concerns Important identified risks

Risk	**What is known**	**Preventability**
Damage to the kidney (Renal function impairment)	Kidney impairment (will normally be determined by your doctor with certain specific blood tests) is a common side effect which may affect 1 to 10 users in 100. Kidney failure, blood loss in urine and protein loss in urine are uncommon side effect which may affect 1 to 10 users in 1,000.	Talk to your doctor, pharmacist or nurse before you are given Zoledronic acid Accord: If you have or have had a kidney problem so that your doctor will give you a lower dose depending on the severity of your kidney problem. It is especially important that you tell your doctor if you are also taking: Thalidomide (a medicine used to treat a certain type of blood cancer involving the bone) or any other medicines which may harm your kidneys

Risk	**What is known**	**Preventability**
Bone damage in the jaw(Osteonecrosis of the jaw)	Anti-angiogenic medicines (used to treat cancer), since the combination of these with zoledronic acid has been associated with reports of osteonecrosis of the jaw. Possible side effects: Pain in the mouth, teeth and/or jaw, swelling or non-healing sores inside the mouth, or jaw, discharge, numbness or a feeling of heaviness in the jaw, or loosening of a tooth. These could be signs of bone damage in the jaw (osteonecrosis) are uncommon side effects which may affects 1 to 10 users in 1,000.	Inform the doctor of the presence of any pain, swelling or numbness of the jaw, a feeling of heaviness in the jaw or loosening of a tooth.Your doctor may recommend a dental examination before you start treatment with Zoledronic Acid Accord. If having dental treatment or are due to undergo dental surgery, tell the dentist if on Zoledronic Acidand inform your doctor about your dental treatment. While being treated with Zoledronic Acid Accord, you should maintain good oral hygiene (including regular teeth brushing) and receive routine dental check-ups. Contact your doctor and dentist immediately if you experience any problems with your mouth or teeth such as

Risk	What is known	Preventability
		loose teeth, pain or swelling, or non-healing of sores or discharge, as these could be signs of a condition called osteonecrosis of the jaw. Tell your doctor and dentist immediately if you experience such symptoms while being treated with Zoledronic Acid Accord or after stopping treatment. Patients who are undergoing chemotherapy and/or radiotherapy, who are taking steroids, who are undergoing dental (teeth) surgery, who do not receive routine dental care, who have gum disease, who are smokers, or who were previously treated with a bisphosphonate (used to treat or prevent bone disorders) may have higher risk of developing osteonecrosis of the jaw.
Flu-like symptoms (Acute	Headache and a flu-like	In most cases no specific

Risk	What is known	Preventability
phase reaction)	syndrome consisting of fever, fatigue, weakness, drowsiness, chills and bone, joint and/or muscle ache. In most cases no specific treatment is required and the symptoms disappear after a short time (couple of hours or days) is a common side effect which may affects 1 to 10 users in 100.	treatment is required and the symptoms disappear after a short time (couple of hours or days).
Reduced levels of calcium in the blood (Hypocalcaemia)	Low level of calcium in the blood is a common side effect which may affects 1 to 10 users in 100. Patients whose blood calcium levels are not too high will also be prescribed calcium and vitamin D supplements to be taken each day. If you have received doses higher than those recommended, you must be carefully monitored by your doctor. This is because you may develop serum electrolyte	If you are being treated to reduce the amount of calcium in your blood, you will normally only be given one infusion of Zoledronic Acid Accord. If your level of calcium falls too low, you may have to be given supplemental calcium by infusion. It is especially important that you tell your doctor if you are also taking: Aminoglycosides (medicines used to treat severe

Risk	What is known	Preventability
	abnormalities (e.g. abnormal levels of calcium)	infections), since the combination of these with bisphosphonates may cause the calcium level in the blood to become too low.
Irregular heart rhythm (Atrial fibrillation)	Irregular heart rhythm (atrial fibrillation) has been seen in patients receiving zoledronic acid for postmenopausal osteoporosis is uncommon side effect which may affects 1 to 10 users in 1,000.	It is currently unclear whether zoledronic acid causes this irregular heart rhythm but you should report it to your doctor if you experience such symptoms after you have received zoledronic acid.
Severe allergic reaction(Anaphylaxis)	Severe allergic reaction: shortness of breath, swelling mainly of the face and throat is uncommon side effect which may affects 1 to 10 users in 1,000.	Do not take the medicine if allergic (hypersensitive) to zoledronic acid, another bisphosphonate (the group of substances to which zoledronic Acid Accord belongs), or any of the other ingredients of this medicine
Inflammation of the tissue around the air sacks of the lungs (Interstitial lung disease)	None	None
Interaction with some	Combination of anti-	Inform the doctor if the patient

Risk	What is known	Preventability
anticancer drugs that can lead to jaw bone damage (Potential interaction with anti-angiogenic drugs that can lead to ONJ)	angiogenic medicines (used to treat cancer), with zoledronic acid has been associated with reports of osteonecrosis of the jaw (ONJ).	is also taking anti-angiogenic medicines (used to treat cancer).

Important potential risks

Risk	What is known
Unusual fracture of the thigh bone (Atypical femoral fractures)	Unusual fracture of the thigh bone particularly in patients on long-term treatment for osteoporosis may occur rarely. Contact the doctor if you experience pain, weakness or discomfort in your thigh, hip or groin as this may be an early indication of a possible fracture of the thigh bone.
Cardiac arrhythmias (irregular heartbeat)	None
Adverse events that develop as a result of problems with the blood vessels inside the brain (Cerebrovascular AEs)	None
Scar tissue that forms in parts of the kidney called glomeruli (Focal Segmental Glomerulosclerosis)	None

Risk	What is known
Poor healing of fractures (Fracture healing impairment)	Poor healing of fractures has also been reported.

Medication errors	Accord zoledronic acid vial and carton will contain the following statements: Carton: Intravenous use Vial: Intravenous use
Risk of off-label use in patients with imperfect bone formation. (Osteogenesis Imperfecta)	In paediatric patients with severe osteogenesis imperfecta, zoledronic acid seems to be associated with more pronounced risks for acute phase reaction (Flu-like symptoms), hypocalcaemia (deduced levels of calcium in the blood) and unexplained tachycardia (rapid heartbeat), in comparison to pamidronate, but this difference declined after subsequent infusions. Limited pharmacokinetic (concerned with the what the body does to a drug) data in children with severe osteogenesis imperfecta suggest that zoledronic acid pharmacokinetics in children aged 3 to 17 years are similar to those in adults at a similar mg/kg dose level. Age, body weight, gender and creatinine clearance appear to have no effect on zoledronic acid systemic exposure.
Interaction with medicines which may harm your kidneys(Potential interaction with drugs that can affect renal function)	The doctor should be informed if the patient is on thalidomide (a medicine used to treat a certain type of blood cancer involving the bone) or any other medicines which may harm your kidneys.

Missing information

Risk	**What is known**
Races other than people from Europe, western Asia, and parts of India and North Africa (Races other than Caucasian)	None

Fertility, Pregnancy and Lactation	Zoledronic Acid Accord should not be given to pregnant female. Tell your doctor if you are pregnant or think that you may be pregnant. Zoledronic acid must not be given if a female is breast-feeding. If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. Studies on animal showed that zoledronic acid did not suggest a definitive effect of zoledronic acid on fertility in humans.
Patients with severe kidney problem (Patients with severe renal impairment)	If there is a kidney problem, the doctor will give a lower dose depending on the severity of your kidney problem. If you have received doses higher than those recommended, you must be carefully monitored by your doctor. This is because you may develop serum electrolyte abnormalities (e.g. changes in kidney function, including severe kidney impairment.
Patients with severe liver problem (Patients with hepatic insufficiency)	As only limited clinical data are available in patients with severe liver insufficiency, no specific recommendations can be given for this patient 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.

The Summary of Product Characteristics for Zoledronic acid Accord can be found in the EPAR page.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). Full details on these conditions can be found in Annex 10 and 11 of this RMP; how they are implemented in each country however will depend upon agreement

between the manufacturer and the national authorities. This additional risk minimisation measures are for the following risk:

- Osteonecrosis of the jaw (ONJ)

Risk minimisation measure: Patient reminder card Patient education
Objective and rationale: Patients to understand the important safety information on side effect called osteonecrosis of the jaw (ONJ) before and during treatment with Zoledronic Acid Accord for cancer-related conditions.
Description: Patient reminder card will inform patients regarding the risk of developing osteonecrosis of the jaw and precautions patients should take to reduce the risk.

VI.2.6 Planned post authorisation development plan

No studies planned.

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

Version	Date	Safety Concern	Comment
3.0	11 April 2018	Following safety concerns have been deleted in this RMP: **Important identified risks**: • "Adverse ocular events" have been deleted. **Missing information:** • "Paediatric patients" and "Paediatric patients with renal impairment" have been deleted.	Risk Management Plan has been updated as per Day 55 comments by CMS (Germany) dated 06-Apr-2018.

2.0	29 November 2016	In this RMP, an important potential risk "cardiac arrhythmias" has been included.	Risk Management Plan has been updated as per Preliminary Variation Assessment Report by RMS (Portugal) dated 07-Nov-2016