6.2 Part VI.2 Elements for a Public Summary

6.2.1 Part VI.2.1 Overview of disease epidemiology

Hypercalcemia is too much calcium in the blood. Hypercalcemia can sometimes develop in people who have cancer. It occurs more often with some cancers like breast, myeloma, lung, kidney, and head and neck cancers than in others like lymphoma. It also occurs more often when the cancer is at an advanced stage and is most commonly associated with widespread bone metastases.

6.2.2 Part VI.2.2 Summary of treatment benefits

Patients with advanced malignancy involving bone are at significant risk, such as the occurrence of tumor-induced hypercalcemia (TIH), which is an elevated level of calcium, and the risk for bone morbidity. TIH in the blood can be a life-threatening complication of malignancy. Bone metastases from solid tumors and osteolytic bone disease in multiple myeloma are associated with considerable skeletal (bone) morbidity, including severe pain, pathologic fracture, the requirement for radiation or surgery to bone (to relieve pain, treat or prevent fracture), nerve root and spinal cord compression. These skeletal complications substantially reduce the quality of life for patients with bone metastases.

Zoledronic acid 4 mg / 5 ml, Concentrate for Solution for Infusion and Zoledronic acid 4 mg / 100 ml, Solution for Infusion has demonstrated efficacy in the treatment of TIH and the prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumor-induced hypercalcemia) in patients with advanced malignancies involving bone.

Efficacy was established in the registration trials conducted with the Novartis product Zometa®, and was confirmed by other completed Novartis clinical trials, and by the medical literature since the time of marketing authorization.

Bisphosphonates have become a standard of care in patients with multiple myeloma and breast cancer, and are recommended in ASCO clinical practice guidelines for these malignancies [Berenson, 2002] [Hilner 2003]. In addition, the clinical benefit of Zometa® in preventing or delaying skeletal-related events has been shown in placebo-controlled trials for prostate cancer, breast cancer, lung cancer, and other solid tumors metastatic to bone.

6.2.3 Part VI.2.3 Unknowns relating to treatment benefits

There is no evidence to suggest that results would be different in any specific population.

6.2.4 Part VI.2.4 Summary of safety concerns

Table 5-5 Important identified risks

Risk	What is known	Preventability
Damage to the kidney (Renal function impairment)	Damage to the kidney could occur after the first dose of Zoledronic acid. However, the risk is higher after long-term use of Zoledronic acid. Dehydration, pre-existing kidney damage, use of Zoledronic acid (or same class drugs) and other drugs toxic to the kidneys may increase the potential for damage to the kidney.	Yes, by assessment of the patient's kidney function and possible dose adjustment.
Bone damage of the jaw (Osteonecrosis of the jaw (ONJ))	Bone damage of the jaw has been reported mostly in cancer patients treated with this drug class (including Zoledronic acid). Many of these patients were also receiving cancer treatment and another medicine called corticosteroids. Many had signs of local infection as well.	Yes, with awareness of the physician and patient of preventability measures (consider a dental examination prior to treatment with bisphosphonates in patients with risk factors such as cancer, anticancer drugs, corticosteroids and poor oral hygiene. While being treated with Zoledronic acid, patients should avoid invasive dental procedures if possible.
Inflammatory reaction (Acute phase reaction (APR))	Inflammatory reaction could include a wide variety of symptoms: fever, muscle pain, headache, extremity pain nausea, vomiting, diarrhea, joint pain and arthritis followed by joint swelling. The occurrence of these symptoms decreases rapidly with each infusion and is not associated with organ damage.	Yes, by careful patient monitoring for the first administration.
Low level of calcium in the blood (Hypocalcemia)	People with a low vitamin D level, and/or not enough calcium in their diet, or a low level of a thyroid hormone called PTH may be more likely to have low calcium in the blood while taking Zoledronic acid. Hypocalcemia seems to occur more often after the first infusion of Zoledronic acid. Events are usually temporary and mild.	Yes, by daily administration of oral calcium supplement and vitamin D and measuring serum calcium and correcting decreased calcium levels, prior to start of Zoledronic acid treatment.
Irregular heartbeat (Atrial fibrillation (AF))	Irregular heartbeat is observed uncommonly (≥1/1,000 to <1/100)	Unknown

Risk	What is known	Preventability
	under therapy with zoledronic acid.	
Allergic reaction (Anaphylaxis)	Allergic reactions have been very rarely seen in studies and after the marketing authorization. These reactions require immediate treatment.	Yes, by close monitoring of the patient when the drug is administered.
Damage of the lung (Interstitial lung disease (ILD))	This risk could impair lung function and the ability of the blood to take up oxygen.	Unknown
Interaction with some anticancer drugs (Interaction with anti-angiogenic drugs)	The use of some anti-cancer drugs (anti-angiogenics) with Zoledronic acid may increase the incidence of bone damage to the jaw in patients with advanced cancer.	Yes, avoid concomitant use when possible.

Table 5-6 Important potential risks

Risk	What is known
Abnormal location of bone fractures (Atypical femoral fracture)	Zoledronic acid events in cancer patients. So it is difficult to establish an association between the reported fractures and the use of Zoledronic acid in these patients who have many risk and factors and complicated health conditions (such as bone cancer, other medications, radiotherapy at fracture site).
Irregular heartbeat other than atrial fibrillation (Cardiac arrhythmias)	Current data shows the most common heart arrhythmia was a fast heartbeat. There were a lot of other risk factors. The severity generally was mild or moderate and did not lead to discontinuation of Zoledronic acid treatment.
Damage in the blood vessels supplying the brain with blood (Cerebrovascular AEs)	There is no clear data showing an increased risk of these events with Zoledronic acid. This damage could lead to permanent disability in patients.
Kidney function damage (Focal Segmental Glomerulosclerosis)	One report was received of this event. This diagnosis has so far been related to another drug in the same class. Close monitoring of the patient is needed.
Damage in how the body helps to repair a broken bone (Fracture healing impairment)	There is a theoretical concern about bone fracture healing with use of this drug class (bisphosphonates). There is no clear evidence of this so far in the use of Zoledronic acid for cancer patients. Bone metastases could also lead to impairment in the healing of fractures.
Off-label use in Osteogenesis imperfecta	The indication of osteogenesis imperfecta is not approved in the EU region and thus considered off-label use for this population.
Medication error	Healthcare professionals and non-healthcare professionals need to be aware of the risk of medication errors and be able to recognize it.
Interaction with products that can significantly affect renal function	With concomitant use of Zoledronic acid and thalidomide (a medicine used to treat a certain type of blood cancer involving the bone) or any other medicines which may harm your kidneys, the risk of renal dysfunction may be increased.

Table 5-7 Missing information

Risk	What is known
People who are not Caucasian (Races other than Caucasian)	Limited experience, although Blacks represented approximately 7% of the safety population in Bone Metastases registration studies. But based on an extensive exposure since Zometa® is on the market (13 years with approximately 5.4 million patients exposed), it has been administered to all races with no change in the safety data.
Reproduction, pregnancy and breast feeding (Fertility, pregnancy and lactation)	Animal studies have shown reproductive toxicity. The effect in human is unknown. Zoledronic acid should not be used during pregnancy. Women of child-bearing potential should avoid becoming pregnant.
Patients with kidney function problems (Patients with severe renal impairment)	Dose adaptation is required for patient with kidney function problem. Patient with severe kidney function were excluded from the studies.
Patients with liver function problems (Patients with hepatic Insufficiency)	Few data available, but animal studies suggest that the drug is not going thought the liver.

6.2.5 Part VI.2.5 Summary of additional risk minimization measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, the risks and recommendations for minimizing 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 minimization measures.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimization measure). Full details on these conditions and the key elements of any educational material can be found in Annex 11 “Mock-up of proposed additional risk minimization measures“; how they are implemented in each country however will depend upon agreement between the manufacturer and the national authorities.

The additional risk minimization measure is for the following risk:

Table 5-8 Summary of additional risk minimization measures for Osteonecrosis of the jaw

Risk minimization measure(s)
Risk minimization measure: Patient education through patient reminder card Objective and rationale: to alert patients on risk of Osteonecrosis of the jaw ***Patient reminder card with following key-content:*** The card will remind patients about: • the risk of osteonecrosis of the jaw during treatment with zoledronic acid; • measures to be taken before and during treatment with zoledronic acid for prevention • Risk factors for development of ONJ • Symptoms of ONJ and informing them to treating physician and dentist

6.2.6 Part VI.2.6 Planned post authorization development plan

N/A

6.2.7 Part VI.2.7 Summary of changes to the Risk Management Plan over time

Table 5-9 Major Changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
3.0	08 Apr 2014	N/A	Transfer of the RMP into the EU RMP Template for Generics with filling of all relevant sections
		N/A	Adjustment of the Sandoz RMP to the Novartis Zometa®-RMP v.9.1 (dated 04 Mar 2014)
		Ocular AEs	- Removed as important identified risk
		Interstitial lung disease	- Change from important potential risk to important identified risk
		Interaction with anti-angiogenic drugs	- Inclusion as important identified risk
		Off-label use in Osteogenesis imperfecta	- Inclusion as important potential risk
		Medication error	- Inclusion as important potential risk
3.1	13 Jan 2015	N/A	According to the day 55 assessment report, with addition of Part II Module S I-IV, VI and VII the RMP was updated to the form for a hybrid application.
		N/A	The RMP was reviewed with regard to the recently completed Novartis Zometa RMP version 9.2.
		Atrial fibrillation	Update of information in Part VI.2.4 Summary of safety concerns
		N/A	Inclusion of information on patients not included in the Novartis clinical trial program in Part VI.2.3 Unknowns relating to treatment benefits.
4.0	21 Sep 2015	Osteonecrosis of jaw	According to the PSUR Assessment EMEA/H/C/PSUSA/00003149/201408, a patient reminder card has been added as additional risk minimization measure. Additionally, the SmPCs and PILs and the marketing authorization status and the post-marketing patient exposure have been updated.
4.1	11 Dec 2015	N/A	Based on RMS Comments on RMP

Version	Date	Safety Concerns	Comment
			for Zoledronic acid 4mg, oncological indication in DE/H/5088/IB/011/G and DE/H/5089/IB/011/G the following changes were made: Part II Module SI to Module SVII were omitted, and corresponding references in Annex 12 were also deleted.
		Osteonecrosis of the jaw	In Part V.1, Part V.3 and Part VI.1.4, the reference to 4.5 of the SmPC was included. In Part V.1 and Part VI.2.5, details on the patient reminder card were updated. In Annex 10, general details on the patient reminder card were updated. In Annex 11, the wording of the patient reminder card was updated. The Checklist in Annex 7 was amended with a question on receipt of the patient reminder card.
		Hypocalcemia	In Part V.1, Part V.3 and Part VI.1.4, the reference to sections 4.2, 4.5 and 4.9 of the SmPC were included, and sections 4.6 and 5.1 of the SmPC were deleted. In Part III.1 and Annex 7, a questionnaire/checklist was included as additional Pharmacovigilance measure.
		Interaction with anti-angiogenic drugs	In Part III.1 and Annex 7, a questionnaire/checklist was included as additional Pharmacovigilance measure.
		N/A	Part VI.2.3 was updated in line with the originator's RMP.
		N/A	Part VI.2.5 "Summary of risk minimization measures by safety concern" was rephrased to "Summary of additional risk minimization measures by safety concern".
		N/A	Annex 2 was updated with the applicable SmPCs and PILs.
4.2	11 Feb 2016	N/A	According to the BfArM request in DE/ H/5088/IB/011/G-DE/H/5089/IB/011/G from 28 Jan 2016, a sentence recommending to

Version	Date	Safety Concerns	Comment
			hand out the package leaflet and the patient reminder card to patients treated with the products was included in the SmPCs in Annex 2 and in the Product information in Part I.