EU Risk Management Plan (RMP) for:

Zometa 4 mg powder and solvent for solution for infusion
Zometa 4 mg/5 ml concentrate for solution for infusion
Zometa 4 mg/100 ml solution for infusion
(Zoledronic acid monohydrate)

RMP version to be assessed as part of this application:

RMP Version Number:	12.2
Data Lock Point for this RMP:	04/04/2025
Date of Final Sign-off:	07/04/2025
Rationale for Submitting an Updated RMP:	The Risk Management Plan (RMP) risks were updated in accordance with the PRAC Rapporteur's proposed Recommendation request from the assessor of PSUSA/3149/202308, which led to the updated of the Summary of Product Characteristics (SmPC) and Product Leaflet (PIL) of the product.
Summary of Significant Changes in this RMP:	The proposal on the changes to the list of safety concerns and missing information topics was presented based on the GVP V-Rev.2 and PSUSA/3149/202308. In addition, all sections have been modified based on the latest RMP template requirements. The summary of safety concerns was updated as following: **Risk upgrade** Atypical femoral fractures were upgraded from Important potential risk" to "Important identified risk"

Details of the Currently Approved RMP:

Version Number:	12.0
Date of final sign-off:	16/09/2019
Date of Approval [End of procedure (EoP)]:	26/03/2021

QPPV name: Rita Ramos

QPPV signature: The content of this RMP has been reviewed and approved by the marketing authorization applicant's QPPV. The electronic signature is available on file.

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ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse event
ATC	Anatomical Therapeutic Chemical
CDS	Core data sheet
CI	Confidence interval
DYD	Defined Yearly Dose
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FDA	Food and Drug Administration
FPP	Farnesyl pyrophosphate
GI	Gastrointestinal
GVP	Guideline on Good Pharmacovigilance Practices
INN	International Non-proprietary Name
iv	Intravenous(ly)
MAH	Marketing Authorization Holder
MAT	Marketing Authorization Transfer
MedDRA	Medical Dictionary for Regulatory Activities
ONJ	Osteonecrosis of the jaw
PRAC	Pharmacovigilance Risk Assessment Committee
PRC	Patient reminder card
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Report
PTHrP	Parathyroid hormone-related protein
PTY	Patient treatment years
PV	Pharmacovigilance
QPPV	Qualified Person Responsible for Pharmacovigilance

RMP	Risk Management Plan
ROW	**Rest of the World**
SmPC	Summary of Product Characteristics
SRE	Skeletal-related events
TIH	Tumour-induced hypercalcaemia
UK	United Kingdom
USA	United States of America
WHO	World Health Organization
ZOL	Zometa

PART I: PRODUCT(S) OVERVIEW

Table 1-1 Table Part I.1 – Product Overview

Active substance(s) **(INN or common name)**	Zoledronic acid monohydrate
Pharmacotherapeutic group(s) (ATC Code)	Drugs affecting bone structure and mineralization, Bisphosphonates. ATC code: M05BA08 (WHO Collaborating Centre for Drug Statistics Methodology 2024).
Marketing Authorisation Holder	Phoenix Labs
Medicinal products to which this RMP refers	One (1)
Invented name(s) in the European Economic Area (EEA)	Zometa
Marketing authorisation (MA) procedure	Centralised
Brief description of the product	**Chemical class:** Zoledronic acid is a third-generation nitrogen-containing bisphosphonates (PubChem 2024).
	Summary of mode of action: Zoledronic acid acts primarily on bone. It is an inhibitor of osteoclastic bone resorption. The selective action of bisphosphonates on bone is based on their high affinity for mineralized bone. Zoledronic acid inhibits Farnesyl pyrophosphate (FPP) synthase, an enzyme in the mevalonate pathway, thereby inhibiting prenylation of key intracellular signalling G-proteins such as Rho, Ras and Rac. The resulting build-up of isopentenyl pyrophosphate leads to apoptosis i.e. programmed cell death. FPP is involved in the regulation of Ras, Rac, and Rho, intracellular G-proteins essential for gene expression; the actin cytoskeleton; membrane trafficking; cell proliferation; cell migration; and cell transformation. Inhibition of FPP production disrupts

	regulation of Ras, Rac, and Rho and thus impairs key cell functions. Uptake of zoledronic acid by osteoclasts therefore results in impaired osteoclast function and apoptosis. In long-term animal studies, zoledronic acid inhibits bone resorption without adversely affecting bone formation, mineralization or mechanical properties. In addition to being a potent inhibitor of bone resorption, zoledronic acid also possesses several antitumor properties that could contribute to its overall efficacy in the treatment of metastatic bone disease. The following properties have been demonstrated in preclinical studies: - In vivo: Inhibition of osteoclastic bone resorption which alters the bone marrow micro-environment, making it less conducive to tumour cell growth, anti-angiogenic activity and anti-pain activity. - In vitro: Inhibition of osteoblast proliferation, direct cytostatic and pro-apoptotic activity on tumour cells, synergistic cytostatic effect with other anti-cancer drugs, anti-adhesion/invasion activity (Phoenix Labs 2024).
Hyperlink to the Product Information	[Current approved SmPC]
Indication(s) in the EEA	**Current:** - Prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumour-induced hypercalcemia) in adult patients with advanced malignancies involving bone. Treatment of adult patients with tumour-induced hypercalcemia (TIH) (Phoenix Labs 2024).
	Proposed: Not applicable.
Dosage in the EEA	**Current:** - ***Prevention of skeletal related events in patients with advanced malignancies involving bone:*** The recommended dose in the prevention of skeletal related events in patients with advanced malignancies involving bone is 4 mg reconstituted zoledronic acid solution or 4 mg zoledronic acid concentrate or 4 mg 'ready to use'

	solution for infusion. Reconstituted solution and concentrate pharmaceutical forms must be further diluted with 100 mL sterile 0.9% w/v sodium chloride or 5% w/v glucose solution before infusion. The final zoledronic acid solution should be administered as an intravenous infusion in no less than 15 minutes every 3 to 4 weeks. Patients should also be administered an oral calcium supplement of 500 mg and 400 IU vitamin D daily (Phoenix Labs 2024). - ***Treatment of TIH:*** The recommended dose in hypercalcemia (albumin-corrected serum calcium[3] 12.0 mg/dL or 3.0 mmol/L) is a single dose of 4 mg zoledronic acid. The concentrate must be further diluted with 100 mL 0.9% w/v sodium chloride or 5% w/v glucose solution, given as a single intravenous infusion of no less than 15 minutes. Patients must be maintained well hydrated prior to and following administration of zoledronic acid (Phoenix Labs 2024).
	Proposed: Not applicable.
Pharmaceutical form(s) and strengths	**Current:** Powder and solvent for solution for infusion 4 mg Concentrate for solution for infusion 4 mg/5 mL Solution for infusion 4 mg/100 mL
	Proposed: Not applicable.
Is/will the product be subject to additional monitoring in the EU?	No

PART II: SAFETY SPECIFICATION

Part II: Module SI – Epidemiology of the indication(s) and target population(s)

1) **Indication:** Prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumour-induced hypercalcemia) in adult patients with advanced malignancies involving bone (Phoenix Labs 2024).

Incidence:

Skeletal related events are a type of composite endpoint defined as pathological fractures, spinal cord compression, bone pain requiring palliative radiotherapy, and orthopaedic surgery (Coleman 1997).

Incidence of skeletal related events by tumour type

Tumour Type	Incidence of skeletal related events (SRE), %	Source reference
Prostate cancer	Almost 3% presented with bone metastases at diagnosis, of whom (43.6%) experienced SRE during the follow-up. For those who were diagnosed without bone metastases 11.5% developed bone metastases along the follow-up, of whom 51.6% suffered for SRE.	Norgaard *et al.* 2010
Breast cancer	SREs were later diagnosed in 43% of those who developed bone metastases along their follow-up and 46% among those who already were diagnosed with bone metastases at the time of breast cancer diagnosis.	Jensen *et al.* 2011

Prevalence of skeletal related events by tumour type

Tumour Type	Incidence of skeletal related events (SRE), %	Source reference
Prostate cancer	SRE are present in 51.7% of cases with a diagnosis of prostate cancer along the follow-up. For men with prostate cancer and bone metastases, 10.0% presented with SRE at the time of the diagnosis of bone metastases and 41.7% along the follow-up.	Oster *et al.* 2013
Breast cancer	SRE are present in 62.2% of cases with a diagnosis of breast cancer along the follow-up. For women with breast cancer and bone metastases, 22.4% presented with SRE at the time of the diagnosis of bone metastases and 40.3% along the follow-up.	Oster *et al.* 2013
Breast cancer	Women with breast cancer and osteolytic bone metastases suffered the following symptoms: - any skeletal complication: 64%, - any radiation to bone: 43%, - radiation to bone for pain relief: 37%, - pathological fracture 52%, - surgery to bone 11%, - spinal cord compression 3%.	Lipton *et al.* 2000

Demographics of the population in the authorised indication -– age, gender, racial and/or ethnic origin and risk factors for the disease: No specific demographic characteristics have been reported in the literature, other than each specific cancer type.

The analysis of patients included in a clinical trial comparing Zoledronate versus Pamidronate showed that Brief Pain Inventory score, Eastern Cooperative Oncology Group Performance status, history of skeletal

related event (SRE), predominance of lytic lesions, and elevated lactate dehydrogenase levels are consistent risk factors for developing a first SRE during zoledronate therapy (Brown *et al.* 2010).

Apart from advanced age, Caucasian race, a history of low-trauma fracture after the age of 50, Body Mass Index <20 kg/m^2, a family history of osteoporosis, current or history of smoking and corticosteroid use have been also identified as a risk factors (Aapro and Coleman 2012).

Main existing treatment options: A publication on the burden of SRE and its treatment presents a thorough literature review and summarized different strategies of treatment (von Moos *et al.* 2013).

Localized radiotherapy from an external beam is frequently used to treat bone lesions and palliate symptoms. Single and multiple fraction radiotherapy in controlling pain, with overall pain response rates of approximately 60% and complete pain response rates of around 20-35% have been reported.

Bone seeking radiopharmaceuticals are an important component of pain palliation in patients with bone metastases. Agents such as Chloride sr-89, Sm-153 lexidronam and rhenium-86 etidronate are suitable for treating lesions of the mixed or blastic type. Response rates range from 45 to 80% with complete response in 10-30% of patients.

The effect of bisphosphonates to reduce the occurrence and delay the onset of SRE is widely studied in different clinical trials (Wong *et al.* 2012). Lastly, denosumab has been approved for treating bone metastases since it neutralized RANK ligand, thereby inhibits osteoclast formation and function, and ultimately bone resorption (von Moos *et al.* 2013).

Recommended treatment options include antiresorptive therapy in women with bone metastases who have plain radiographic evidence of bone destruction and suggest that therapy should continue for at least 2 years, with treatment thereafter based on individual risk assessment. Treatments include zoledronic acid (4 mg iv every 3-4 weeks), pamidronate (90 mg iv every 3-4 weeks) denosumab (120 mg subcutaneously every 4 weeks) (Van Poznak *et al.* 2011).

Natural history of the indicated condition in the untreated population including mortality and morbidity: The study performed by (Norgaard *et al*. 2010) showed that mortality for prostate cancer males with SRE was highest in all three stages of the disease.

Mortality in patients with prostate cancer in 1993 to 2003 cohort by stage of diagnosis

	Deaths/1000 person-years (95% CI)	
	Follow-up 1 year	**Follow-up 2-5 years**
Localized		
No bone metastases	74.5 (65.1-85.2)	77.0 (71.4-83.0)
Bone metastases + SRE	1262.8 (602.1-2649.1)	1048.7 (853.9-1287.9)
Regional		
No bone metastases	143.1 (114.8-178.4)	139.3 (120.9-160.4)
Bone metastases + SRE	1303.5 (621.4-2734.2)	1007.6 (739.1-1373.7)
Distant		
No bone metastases	331.1 (302.5-362.5)	266.3 (244.9-289.6)
Bone metastases + SRE	763.9 (619.2-942.6)	1010.8 (912.0-1120.4)
SRE= Skeletal related events		

In this study, 1-year survival rates in men with prostate cancer without bone metastases was 87%, 47% in those with bone metastases but not SRE and only 40% in those with bone metastases and SRE.

The analysis of 98260 elderly women with breast cancer in the SEER-Medicare database in the US showed that women with bone metastases had HR of death 4.9 (95% CI: 4.7, 5.1) and for those with bone metastases plus SRE HR of death was calculated 6.2 (95% CI: 5.9, 6.5) (Sathiakumar *et al.* 2012).

A retrospective analysis of US claims database showed that in women with breast cancer and bone metastases plus SRE mortality was increased four to five times as compared with women without SREs (36.26 rate per 100 person-years vs. 6.48 rate per 100 person-years) (Henk and Kaura 2012).

Important co-morbidities: Results from a randomized, phase III, double blind placebo-controlled trial on the long-term efficacy and safety of Zoledronic acid (Rosen *et al.* 2004), gave the following co-morbidities in both the treated group and the placebo group.

Co-morbidity of target population – patients with advanced malignancies involving bone

	Incidence (%)	
Co-morbidity	**Zoledronic acid 4 mg group**	**Placebo group**
Bone pain	50.9	60.7
Nausea	42.3	36.4
Anaemia	33.2	34.8
Emesis	33.2	30.4
Constipation	30.9	38.1
Dyspnoea NOS	37.0	30.0
Fatigue	30.6	30.0
Pyrexia	27.9	23.5
Aggravated malignancy	29.1	25.9
Source: Rosen *et al.* 2004		

Co-morbidities in patients with incident prostate cancer from 1999 to 2007 in Denmark

	Entire cohort	**Bone metastases cohort**	**Bone metastases + SRE cohort**
Myocardial infarction	6.0	6.9	5.3
Congestive Heart Failure	6.0	6.1	4.0
Peripheral Vascular Disease	5.0	5.4	4.1
Cerebrovascular disease	9.8	4.8	7.3
Dementia	1.0	8.9	0.6
Chronic Pulmonary Disease	7.6	0.5	4.6
Connective Tissue disease	2.1	6.0	2.0
Ulcer	4.1	2.1	3.1
Mild liver disease	0.6	3.5	0.8
Diabetes type I and II	5.1	0.7	3.9
Any tumour	7.5	2.1	5.9
Source: Norgaard *et al.* 2010			

2) **Indication:** Treatment of adult patients with tumour-induced hypercalcemia (TIH). (Phoenix Labs 2024).

Incidence: Hypercalcemia was identified in the early 1920s as a metabolic disorder complicating cancer. Its occurrence is particularly common in hospitalized patients whose underlying disease is usually more advanced. The incidence of hypercalcemia varies depending on the type of cancer and its phase.

Hypercalcemia is the most frequent metabolic complication of breast cancer. It occurs during the disease in 30 to 40% of patients (Muggia 1990). It usually occurs late in the disease and is most associated with widespread osteolytic metastases. In patients with lung cancer hypercalcemia ranges from 12.5 to 35% (Muggia 1990). For patients with head and neck cancer the incidence of hypercalcemia had been reported between 2.9 and 25%. In renal cell carcinoma, hypercalcemia has been reported to occur in 3 to 17% of cases. Virtually all patients with Multiple Myeloma have extensive osteolytic bone destruction and approximately 20 to 40% develop hypercalcemia at some point during their disease. The occurrence of hypercalcemia in association with lymphoma is relatively uncommon, occurring in only 0.3 to 4% of patients (Muggia 1990).

Within each disease type, the incidence of hypercalcemia varies greatly in reported series (Kaplan 2010).

Incidence of hypercalcemia by tumour type

Tumour Type	Incidence (%) of hypercalcemia of Malignancy	Source reference
Breast (with bone metastases)	30-40	Kaplan 2010
Multiple myeloma	20-40	
Squamous cell carcinoma of lung	12.5-35	
Squamous cell carcinoma of head and neck	2.9-25	
Renal cell carcinoma	3-17	
Lymphomas; Hodgkin lymphoma	0.6-5.4	
Non-Hodgkin lymphoma, high-grade	14-33	
T-cell lymphoma (human T-cell, lymphotropic virus type 1)	50	
Other malignancies: ovary, liver pancreas, oesophagus, cervix	7	
Unknown primary	7	

Types of hypercalcemia associated with cancer

Type Frequency	Frequency	Bone Metastases	Causal Agent	Typical Tumours
Local osteolytic hypercalcemia	20	6.9	Cytokines, chemokines, parathyroid hormone-related protein (PTHrP)	Breast cancer, Multiple myeloma, lymphoma
Humoral hypercalcemia of malignancy	80	Minimal or absent	PTHrP	Squamous-cell cancer, renal cancer, ovarian cancer, endometrial cancer, Human T-lymphotropic virus - associated lymphoma, breast cancer
1.25(OH)2D- secreting lymphomas	< 1	Variable	1.25(OH)2 D	Lymphoma all types
Ectopic hyperparathyroidism	< 1	Variable	Parathyroid hormone	Variable
Source: Steward 2005				

Demographics of the population in the authorized indication – age, gender, racial and/or ethnic origin and risk factors for the disease: The demographics of TIH are related to the demographic characteristics of each type of cancer. TIH can occur also in children with cancer, but with much less frequency (0.5%-1%) (Kerdudo *et al.* 2005).

Immobility is associated with an increase in resorption of calcium from bone. Dehydration, anorexia, nausea, and vomiting that exacerbate dehydration reduce renal calcium excretion. Hormonal therapy (oestrogens, antioestrogens, androgens, and progestins) may precipitate hypercalcemia. Thiazide diuretics increase renal calcium reabsorption and may precipitate or exacerbate hypercalcemia (Coleman 1997).

Hematologic malignancies may stimulate osteoclastic bone resorption through the production of cytokines such as TNF-alpha and -beta and interleukin-1 and -6, formerly referred to as osteoclast activating factor(s) (Warrell 1992).

The main existing treatment options: Treatment for hypercalcemia should be aimed both at lowering the serum calcium concentration and, if possible, treating the underlying disease. Effective treatments reduce serum calcium by inhibiting bone resorption, increasing urinary calcium excretion, or decreasing intestinal calcium absorption. The optimal choice varies with the cause and severity of hypercalcemia.

The degree of hypercalcemia, along with the rate of rise of serum calcium concentration, often determines symptoms and the urgency of therapy. The therapeutic approach should reflect these differences (Shane and Berenson 2013).

Mild hypercalcemia — Patients with asymptomatic or mildly symptomatic hypercalcemia [calcium <12 mg/dL (3 mmol/L)] do not require immediate treatment. However, they should be advised to avoid factors that can aggravate hypercalcemia, including thiazide diuretics and lithium carbonate therapy, volume depletion, prolonged bed rest or inactivity, and a high calcium diet (>1000 mg/day). Adequate hydration (at least six to eight glasses of water per day) is recommended to minimize the risk of nephrolithiasis. Additional therapy depends mostly upon the cause of the hypercalcemia.

Moderate hypercalcemia — Asymptomatic or mildly symptomatic individuals with chronic moderate hypercalcemia (calcium between 12 and 14 mg/dL [3 to 3.5 mmol/L]) may not require immediate therapy. However, they should follow the same precautions described for mild hypercalcemia. It is important to note that an acute rise to these concentrations may cause marked changes in sensorium, which requires more aggressive therapy. These patients are typically treated with saline hydration and bisphosphonates, as described for severe hypercalcemia.

Severe hypercalcemia — Patients with calcium > 14 mg/dL (3.5 mmol/L) require more aggressive therapy. The acute therapy of such patients consists of a three-pronged approach:

- Volume expansion with isotonic saline at an initial rate of 200 to 300 mL/hour that is then adjusted to maintain the urine output at 100 to 150 mL/hour. Loop diuretics are not recommended to directly increase calcium excretion unless accompanied by renal failure or heart failure, because of potential complications. Drugs that inhibit bone resorption are better option for hypercalcemia related to malignancy and bone involvement.
- Administration of salmon calcitonin (4 IU/kg) and repeat measurement of serum calcium in several hours. If a hypocalcaemia response is noted, then the patient is calcitonin sensitive, and the calcitonin can be repeated every 6 to 12 hours (4 to 8 international units/kg). Typically administer calcitonin (along with a bisphosphonate) in patients with calcium > 14 mg/dL who are also symptomatic.
- The concurrent administration of zoledronic acid (4 mg IV over 15 minutes) or pamidronate (60 to 90 mg over two hours), preferably zoledronic acid, because it is superior to pamidronate in reversing hypercalcemia related to malignancy.

The administration of calcitonin plus saline should result in substantial reduction in serum calcium concentrations within 12 to 48 hours. The bisphosphonate will be effective by the second to fourth day, thereby maintaining control of the hypercalcemia.

Follow-up therapy is aimed at preventing recurrence of hypercalcemia. In patients with hypercalcemia of malignancy, progressive hypercalcemia will inevitably accompany tumour progression, and therefore the underlying disease causing the hypercalcemia should be treated, if possible. Many patients with malignancy may also have metastatic bone disease and will receive intravenous zoledronic acid or pamidronate every three to four weeks as part of their treatment to prevent skeletal complications. As a result, recurrent hypercalcemia will be prevented.

Additional, more aggressive measures are necessary in the rare patient with very severe, symptomatic hypercalcemia. Haemodialysis should be considered, in addition to the above treatments, in patients who have serum calcium concentrations in the range of 18 to 20 mg/dL (4.5 to 5 mmol/L) and neurologic symptoms but a stable circulation.

In addition to bisphosphonates, osteoclast inhibition can also be achieved by targeting receptor activator of nuclear factor kappa B ligand, a key component in the pathway for osteoclast formation and activation. Expression of receptor activator of nuclear factor kappa B ligand in bone is also thought to contribute to the development of bone metastases by binding to its receptor (receptor activator of nuclear factor kappa B, RANK) on the surface of tumour cells.

Natural history of the indicated condition in the population, including mortality and morbidity: Hypercalcemia generally develops as a late complication of malignancy; its appearance has grave prognostic significance. It remains unclear, however, whether death is associated with hypercalcaemic crisis (uncontrolled or recurrent progressive hypercalcemia) or with advanced disease. It has been observed that 50% of patients with hypercalcemia die within 1 month and 75% within 3 months after starting hypocalcaemia treatment (Blomqvist 1986). In the same study, patients with hypercalcemia who responded to specific antineoplastic treatment were found to have a slightly greater survival advantage over non-responders. Other prognostic variables have shown to correlate with longer survival included serum albumin concentration (direct correlation), serum calcium concentrations after treatment (inverse correlation), and age (inverse correlation). In contrast with their modest effect on survival, marked but differential response rates were observed after hypocalcaemia treatments as a factor of symptom type. The most substantial improvements occurred in renal and central nervous system–related symptoms (nausea, vomiting, and constipation). Symptoms of anorexia, malaise, and fatigue improved, but less completely (Ralston *et al.* 1990).

In a study on lung cancer patients the median survival time after development of hypercalcemia as a complication of carcinoma of the lung was one month (range 1 week to 10 months) (Coggeshall *et al.* 1986). Another study in the UK with 126 consecutive patients with cancer- associated hypercalcemia found the median survival of 30 days (Ralston *et al.* 1990).

Important co-morbidities: There is little correlation between the presenting symptoms of hypercalcemia and serum calcium concentrations. Rapid diagnosis of hypercalcemia may be complicated because

symptoms associated with hypercalcemia are characteristically nonspecific and are easily attributed to chronic or terminal illness.

Few patients experience all the symptoms that have been associated with hypercalcemia, and some patients may not experience any symptoms. Patients with corrected total serum calcium concentrations higher than 14 mg/dL (> 7.0 mEq/L or 3.49 mmol/L) are generally symptomatic. It must be emphasized that clinical manifestations are closely related to the rapidity of hypercalcemia onset. Some patients develop signs and symptoms when calcium is only slightly elevated, while others with long-standing hypercalcemia may tolerate serum calcium levels higher than 13 mg/dL (>6.5 mEq/L or 3.24 mmol/L) with few symptoms. Neuromuscular manifestations are generally more marked in older patients than in young patients. One author observed that malaise and fatigue were the most common complaints at patient presentation, followed by (in order of decreasing prevalence rate) varying degrees of obtundation, anorexia, pain, polyuria-polydipsia, constipation, nausea, and vomiting.

Symptom prevalence among patients treated for hypercalcemia of malignancy stratified by corrected serum total calcium concentration at presentation

Symptoms	Prevalence (%) by serum calcium concentration	
	<3.5 mmol/L	≥ 3.5 mml/L
Central Nervous System	41	80
Constipation	21	25
Malaise-fatigue	65	50
Anorexia	47	59
Nausea and/or vomiting	22	30
Polyuria and/or polydipsia	34	35
Pain	51	35
Source: Ralston *et al.* 1990		

Results from a randomized, phase III, double blind placebo-controlled trial on the long-term efficacy and safety of Zoledronic acid (Rosen *et al.* 2004), gave the following co-morbidities in both the treated group and the placebo group.

Co-morbidity of target population – patients with advanced malignancies involving bone

	Incidence (%)	
Co-morbidity	**Zoledronic acid 4 mg group**	**Placebo group**
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Co-morbidities in patients with incident prostate cancer from 1999 to 2007 in Denmark

	Entire cohort	**Bone metastases cohort**	**Bone metastases + SRE cohort**
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Dementia	1.0	8.9	0.6
Chronic Pulmonary Disease	7.6	0.5	4.6
Connective Tissue disease	2.1	6.0	2.0
Ulcer	4.1	2.1	3.1
Mild liver disease	0.6	3.5	0.8
Diabetes type I and II	5.1	0.7	3.9
Any tumour	7.5	2.1	5.9
Source: Norgaard *et al.* 2010			

Part II: Module SII – Non-clinical part of the safety specification

Key safety findings from non-clinical studies and relevance to human usage

Key safety findings (from non-clinical studies)	Relevance to human usage
Toxicity	
Acute or repeat-dose toxicity studies	
Renal Effects: Renal effects were observed in the animal toxicology studies, including renal tubular necrosis/regeneration and inflammation associated with elevated urea and serum creatinine. However, the margin of safety after both acute and repeat-dose parenteral (intravenous, subcutaneous) exposure in rats and dogs, did not indicate renal effects at cumulative doses equivalent to or exceeding the highest intended human dose of 4 mg to treat tumour-induced hypercalcemia.	Risk of renal injury in man leading to compromised renal function. Compromised renal function can be monitored in the clinic and risk management procedures are in place.
Bone effects: Bone changes (non-proliferative hyperostosis) reflecting the pharmacological activity of zoledronic acid was observed in most of the repeat-dose studies.	Bone changes constitute expected Pharmacological anti-resorptive effects and may occur in patients on Zometa. Such changes are not considered adverse.
Toxicity in soft tissues: Zoledronic acid effects were observed in soft tissues including liver, gastrointestinal (GI) tract, spleen and lung (lung effects are described further below). These organ/tissue alterations were a consequence of locally high concentrations of the compound and were observed at high doses in preclinical studies. The findings included (but were not limited to) inflammation, haemorrhage and erosions in the GI tract, hepatocellular necrosis, inflammatory lesions in the lung, splenic inflammation and haemorrhage, and severe local skin inflammation at injection sites, particularly in the iv studies.	These effects are not deemed to be clinically relevant as they occur at doses and cumulative exposures much higher than used in the clinic. In addition, clinical data over many years of use of Zometa has not raised any cause for concern on any of these findings.
Lung findings: Lung findings worthy of mention were described in three repeat-dose, non-clinical toxicology studies ranging from 10 days to 3 months duration. In each case, these findings consisted of focal inflammatory cell infiltrates (mostly mononuclear, and of minimal - slight severity) that in one case specifically related to inflammation at other sites (injection site and renal inflammation). Similar findings were also seen in controls (lower severity and/or incidence); they may represent exacerbation of background changes. In addition, there was no fibrotic component of the pulmonary interstitium even in long-term studies of up to 1 year. No reveal evidence of pulmonary effects including pulmonary fibrosis has been reported in non-clinical literature to date.	The cumulative doses at which these inflammatory lesions occurred represented many multiples of the monthly 4-mg human dose. Hence, these effects are not deemed to be clinically relevant. In addition, since there was no fibrotic component observed in the lungs, it is unlikely that the changes represent a form of interstitial lung disease as described in humans.

Reproductive/developmental toxicity	
Teratogenicity: Teratology studies were performed in two species, both via subcutaneous administration of zoledronic acid. Teratogenicity was observed in the rat at doses ≥ 0.2 mg/kg/day and was manifested by external, visceral and skeletal malformations. Dystocia was observed at the lowest dose (0.01 mg/kg/day) tested in rats. No teratological or embryo/foetal effects were observed in the rabbit, although maternal toxicity was marked at 0.1 mg/kg/day. Adverse maternal effects were associated with and may have been caused by drug-induced hypocalcaemia.	Potential for teratogenicity, fetotoxicity and adverse effects on fertility in patients.
Fertility: Zoledronic acid was evaluated in rats for potential adverse effects on fertility of the parental and F1 generation. This resulted in exaggerated pharmacological effects considered related to the compound's inhibition of skeletal calcium mobilization, resulting in periparturient hypocalcaemia, a bisphosphonate class effect, dystocia and early termination of the study. Thus, these results precluded determining a definitive effect on fertility in animals	Potential for teratogenicity, fetotoxicity and adverse effects on fertility in patients.
Genotoxicity: There was no evidence for a mutagenic potential of zoledronic acid in a series of standard in vitro and in vivo genotoxicity studies.	No human risk identified.
Carcinogenicity: In standard carcinogenicity studies in mice and rats, zoledronic acid showed no carcinogenic potential when administered by the oral route. In these studies, systemic exposure to zoledronic acid was not measured but the pharmacological bone changes gave clear evidence of systemic exposure to zoledronic acid in both species.	No human risk identified.
Source: non-clinical overview 2013, PSUR (reporting interval: 01-Sep-2011 to 31-Aug-2012)	

Part II: Module SIII – Clinical trial exposure

For the indication of treatment of TIH, patients received only one infusion during the core phase, therefore no exposure is summarized in the following tables. Because of a single infusion being administered for this indication, a detailed breakdown by duration is not applicable.

The following tables summarize clinical trial patient exposure to **Zometa 4 mg**. The data include four registration trials for the indication of SRE prevention in advanced malignancy involving bone.

Duration of exposure

Duration	SREs N=1099
Less than 6 months	386 (35.1)
6 - < 12 months	341 (31.0)
12 - < 18 months	139 (12.6)
18 - < 24 months	194 (17.7)
24 - < 30 months	38 (3.5)
≥ 30 months	1 (0.1)
Patient-years	947.9
Zometa EU RMP version 12.0	

Exposure by age group and gender

		SREs N=1099	
Age	**Sex**	**Patients n (%)**	**Patient-years**
Total	**Total**	**1099 (100)**	**947.9**
	Male	494 (44.9)	396.9
	Female	605 (55.1)	551.0
18 - < 65 years	**Total**	**583 (53.0)**	**527.4**
≥ 65 years	**Total**	**516 (47.0)**	**420.5**
Zometa EU RMP version 12.0			

Exposure by race

		SREs N=1099
Race	**Patients n (%)**	**Patient-years**
Caucasian	962 (87.53)	831.0
Black	77 (7.01)	66.5
Asian	18 (1.64)	13.8
Other	42 (3.82)	36.5
Zometa EU RMP version 12.0		

Part II: Module SIV – Populations not studied in clinical trials

Important exclusion criteria in pivotal studies in the development program

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
Hypersensitivity	Patients predisposed to or with known prior history of zoledronic acid hypersensitivity may experience symptoms including, but not limited to: anaphylactic reaction/shock, urticaria, dyspnoea, flushing, chest pain or angioedema. Therefore, Zometa should not be administered in these patients.	No	There were no severe effects observed during the clinical development. The adverse drug reaction (ADR): "Hypersensitivity" is included in the label. It is also mentioned as a contraindication, which means that the risk is managed, and no new relevant data are expected.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
Breastfeeding	It is not known whether zoledronic acid is not excreted in human milk.	No	Zometa is contraindicated breastfeeding women. Use in lactation was under close monitoring in Zometa PSUR and RMP as a missing information (fertility, pregnancy, and lactation). Post-marketing experience (safety database and literature) of over 18 years did not reveal any new safety information on use of Zometa during lactation. There is no reasonable expectation that this topic could be further characterized hence removed as a missing information.
Pregnancy	With limited safety, pregnant females were not exposed to zoledronic acid.	No	Zometa should not be used during pregnancy. Use in pregnancy was under close monitoring in Zometa PSUR and RMP as a missing information. Based on animal reproductive toxicity study results (teratogenic in the rat), the MAH proposes to recategorize the missing information as an Important potential risk and rename it as "Teratogenicity".
Treatment with bisphosphonates at any time during the 12 months prior to Visit 1.	Efficacy related	No	No impact on safety and difficult to retrieve this information in post-marketing setting.
Corrected (adjusted for serum albumin) serum calcium < 8.0 mg/dL (2.00 mmol/L) or > 12 mg/dL (3.00 mmol/L) at Visit 1.	At risk of developing Hypocalcaemia	No	The risk of hypocalcaemia is already established.
Serum creatinine > 3 mg/dL (265.2 µmol/L)	At risk of renal impairment	No	There are adequate safety data. The use of Zometa is not recommended in this population.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
Total bilirubin > 2.5 g/dL (43 mol/L).	Limited data on safety and efficacy in hepatic impairment patients	No	Zoledronic acid does not inhibit human P450 enzymes in vitro, shows no biotransformation and in animal studies < 3% of the administered dose was recovered in the faeces, suggesting no relevant role of liver function in the pharmacokinetics of zoledronic acid.

Part II: Module SV – Post-authorisation experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

An estimate of patient exposure is calculated based on worldwide sales volume in milligrams (mg) of active substance sold cumulatively since the first launch.

A conservative estimate of the Defined Yearly Dose (DYD) for Zometa is approximately 24 mg (0.000024 kg) per patient. This accounts for the possible maximum exposure, by considered as average defined yearly dose due to multiple frequencies of Zometa infusions as per the SmPC, based on underlying indications (every 3-4 weekly or every 6 monthly or single infusion, with onset of treatment effect normally being 2-3 months). The post-marketing exposure presented below is for all the worldwide approved indications and not limited only to the EU approved indications.

The estimated exposure in Patient-Treatment-Years (PTYs) was calculated based on the below formula:

PTY = Total amount sold in mg / DYD

SV.1.2 Exposure

The cumulative worldwide sales volume since the first launch of Zometa, from post-marketing (non-clinical trial), considering sales before and after Marketing Authorization Transfer to Phoenix Labs, is 26.763 kg of active substance.

The patient exposure based on demographics (i.e. age, gender, race and ethnicity) could not be estimated; therefore, it is not possible to estimate the patient exposure in by populations is unavailable.

Till the 28-February-2025, the cumulative patient exposure, since the international birth date of the product, is estimated to be of the product is estimated to be approximately 1 115 141.17 million PTY.

The estimated exposure based on the above formula is provided in the below table:

Country	Nature and contents of container	Covered Period	Sold units	Amount Sold (mg)	PTD	PTY
EEA	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/10/2000 to 31/08/2020	2 678 798	10 715 192	2 678 798	446 466.33
USA and Canada	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/10/2000 to 31/08/2020	1 642 937	6571748	164 2937	273 822.83
Japan	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/10/2000 to 31/08/2020	[redacted]			
ROW	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/10/2000 to 31/08/2020	153 2431	6 129 724	1532431	255 405.17
Austria	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025	[redacted]			
	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/100ml Solution for Infusion	From 01/09/2020 to 28/02/2025				
Belgium	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/100ml Solution for Infusion	From 01/09/2020 to 28/02/2025				
Bulgaria	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/100ml Solution for Infusion	From 01/09/2020 to 28/02/2025				
Croatia	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/100ml Solution for Infusion	From 01/09/2020 to 28/02/2025				

Country	Nature and contents of container	Covered Period	Sold units	Amount Sold (mg)	PTD	PTY
Cyprus	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025	[redacted]			
	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/100ml Solution for Infusion	From 01/09/2020 to 28/02/2025				
Czechia	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/100ml Solution for Infusion	From 01/09/2020 to 28/02/2025				
Estonia	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/100ml Solution for Infusion	From 01/09/2020 to 28/02/2025				
Finland	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/100ml Solution for Infusion	From 01/09/2020 to 28/02/2025				
France	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/100ml Solution for Infusion	From 01/09/2020 to 28/02/2025				
Germany	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				

Country	Nature and contents of container	Covered Period	Sold units	Amount Sold (mg)	PTD	PTY
	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025	[redacted]			
	Zometa 4 mg/100ml Solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
Great Britain	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/100ml Solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
Greece	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/100ml Solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
Hungary	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/100ml Solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
Iceland	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/100ml Solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
Ireland	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				

Country	Nature and contents of container	Covered Period	Sold units	Amount Sold (mg)	PTD	PTY
	Zometa 4 mg/100ml Solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
Italy	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/100ml Solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
Latvia	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/100ml Solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
Lithuania	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/100ml Solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
Luxembourg	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/100ml Solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
Malta	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/100ml Solution for Infusion	From 01/09/2020 to 28/02/2025				

Country	Nature and contents of container	Covered Period	Sold units	Amount Sold (mg)	PTD	PTY
	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025	[redacted]			
Mauritius	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/100ml Solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
Montenegro / Serbia	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/100ml Solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
Netherlands	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/100ml Solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
Norway	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/100ml Solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
Poland	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/100ml Solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				

Country	Nature and contents of container	Covered Period	Sold units	Amount Sold (mg)	PTD	PTY
Portugal	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025	[redacted]			
	Zometa 4 mg/100ml Solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
Romania	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/100ml Solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
Slovakia	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/100ml Solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
Slovenia	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/100ml Solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
Spain	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/100ml Solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
Sweden	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				

Country	Nature and contents of container	Covered Period	Sold units	Amount Sold (mg)	PTD	PTY
	Zometa 4 mg/100ml Solution for Infusion	From 01/09/2020 to 28/02/2025				
	Zometa 4 mg/5ml Concentrate for solution for Infusion	From 01/09/2020 to 28/02/2025				
Total		From 01/10/2000 to 28/02/2025	6 690 847	26 763 388	6 690 847	1 115 141.17

EEA – European Economic Area; USA – United Stated of America; ROW – Rest of the World; PTD – Patient-Treatment-Days; PTY – Patient-Treatment-Years .

Part II: Module SVI – Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Abuse potential is not a known risk of bisphosphonates. While no clinical studies have been carried out to specifically investigate abuse potential, no evidence has emerged from clinical trials or from the post-marketing experience which would suggest a potential for abuse or dependence with zoledronic acid.

Part II: Module SVII - Identified and potential risks

Not applicable.

SVII.1 Identification of safety concerns in the initial RMP submission

Not applicable.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

All the proposed changes to the list of safety concerns and missing information topics are based on GVP Module V Rev.2.

The safety concerns that were removed or reclassified since the previous RMP version are described in below.

Description of the changes done in the list of the safety concerns since the previous RMP version

Safety concerns	Previous Classification	Reclassification or removed	Rationale*
Atypical femoral fractures	Important potential risk	Atypical femoral fractures upgraded from Important potential risk" to "Important identified risk"	In the PRAC AR (EMEA/H/C/PSUSA/00003149/202008 dated 09th April 2021) for the last Zometa PSUR, the rapporteur mentioned that "a review of cumulative data provided evidence of causal association between the risk of occurrence of Atypical femoral fractures with Zometa administration. Atypical subtrochanteric and diaphyseal femoral fractures are listed as ADRs in the EU SmPC. Therefore, the upgrade of the important potential risk "Atypical femoral fractures" to an important identified risk is endorsed. Furthermore, Furthermore, as an outcome of PRAC conclusions of PSUSA/3149/ 202308, MAH proposes to rename this risk atypical subtrochanteric/femoral fractures avascular necrosis (AVN)/fracture non or delayed union fracture healing impairment to atypical femoral fractures.
*Zometa PSUR (reporting interval: 01-Sep-2020 to 31-Aug-2023) and GVP V-rev 2			

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important identified risks:

Osteonecrosis of the jaw: Other details – No statistical outputs are available.

Osteonecrosis of the jaw	Details
Potential mechanisms	Several potential mechanisms through which bisphosphonates may contribute to the development of osteonecrosis of the jaw (ONJ) have been raised: - Preferential localization of bisphosphonate in the jaw bones compared with other skeletal sites. - Greater sensitivity of jawbone turnover to bisphosphonate inhibition compared to other skeletal sites. - Accumulation of bisphosphonate in the jaw in the presence of periodontal disease, or following tooth extraction or other dental trauma, and altered bone healing response. - Alteration by bisphosphonate therapy of the normal microbial flora in the oral cavity. - Inhibition of the host immune response favouring mucosal or bone infection and the development of osteomyelitis. - Synergistic interaction between bisphosphonate and other concomitant medications (e.g. anti-angiogenic drugs, steroids, cytotoxic chemotherapy, thalidomide, etc.). However, the pathogenesis of ONJ remains unclear, and there is very limited evidence in support of the often cited, interesting but unproven hypotheses related to the pathogenesis of ONJ. A causal relationship between ONJ and Zometa has not been established.
Evidence source(s) and strength of evidence	Current evidence is based on the review of published literatures and post-marketing cases from safety database. The event is listed in the label.

Osteonecrosis of the jaw	Details
Characterization of the risk	In the Zometa Clinical trials, the frequency of ONJ was found to be uncommon. Based on the available information, ONJ is a reversible condition with appropriate management and does not cause permanent organ or tissue damage. Rare cases will require a dental procedure to accelerate healing. Depending on the stage of ONJ, management include non-surgical management such as antimicrobial therapy (rinses to systemic antibiotics) and analgesics to surgical debridement and excision. Temporary interruption of zoledronic acid treatment should be considered until the condition resolves and contributing risk factors are mitigated where possible. **Data from Study CZOL446EUS122/SWOG Study (category 3 study)** The primary objective of this prospective observational multicentre cohort study was to estimate the cumulative incidence of ONJ at 3-years in cancer patients with bone metastasis receiving zoledronic acid treatment. The osteoclast inhibition therapy, other cancer, and dental care was performed as clinically indicated in order to best represent academic and community-based care. A baseline dental exam was recommended but was not mandatory. Among the 3491 evaluable patients, 87 cases of ONJ diagnosis were confirmed. The overall estimated cumulative incidence of confirmed ONJ at 3-year was 2.8% (95% CI: 2.3-3.5%). The rates were 0.8% at year 1 and 2.0% at year 2. Rates of 3-year confirmed ONJ were highest in myeloma patients (4.3%; 95% CI, 2.8%-6.4%) and lowest in breast cancer patients (2.4%; 95% CI, 1.5%-3.4%), Clinical Overview-SWOG report. Cases of confirmed ONJ were statistically significantly higher in patients with multiple myeloma (p=0.03) than other cancers combined. The results were similar when confirmed plus suspicious ONJ were considered (p=0.04), Clinical Overview-SWOG report.
Risk factors and risk groups	ONJ has multiple risk factors including a diagnosis of cancer, concomitant therapies (e.g. chemotherapy, radiotherapy, corticosteroids) and co-morbid conditions (e.g. anaemia, coagulopathies, infection, pre-existing dental disease and poor oral cavity hygiene). Data suggest a greater frequency of reports of ONJ based on tumour type (advanced breast cancer, multiple myeloma).
Preventability	As stated in the label, a dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in

Osteonecrosis of the jaw	Details
	patients with concomitant risk factors (e.g. cancer, chemotherapy, corticosteroids, poor oral hygiene). While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop ONJ 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 ONJ. The start of treatment or of a new course of treatment should be delayed in patients with unhealed open soft tissue lesions in the mouth, except in medical emergency situations. The management plan for patients who develop ONJ should be set up in close collaboration between the treating physician and a dentist or oral surgeon with expertise in ONJ. Temporary interruption of zoledronic acid treatment should be considered until the condition resolves and contributing risk factors are mitigated where possible. The clinical judgment of the treating physician should guide the management plan of each patient based on the individual benefit-risk assessment. Recent data provide evidence that ONJ risk minimization programs inclusive of dental examination and preventive dentistry prior to initiation of Zometa therapy, good oral hygiene, and/or prophylactic antibiotics for dental procedures during Zometa therapy may reduce the risk of developing ONJ in oncology patients receiving Zometa therapy (Ripamonti *et al* 2009, Dimopoulos *et al* 2009, Montefusco *et al* 2007).
Impact on the benefit-risk balance of the product	**Modest.** The patient's underlying cancer is a significant risk factor for ONJ. There are risk minimization measures (Patient Reminder Card) in place to provide key precautionary messages to the patients. This risk is appropriately communicated in the label with risk minimization measures described. The review of the data received during the reporting interval did not provide any new relevant safety information pertaining to the important identified risk of ONJ. There was no increase in frequency or severity of ONJ.
Public health impact	**Low.** The incidence of ONJ in the overall population of Zometa-treated patients is uncommon. Furthermore, there are multiple risk factors in addition to zoledronic acid. Current risk minimization measures include Patient Reminder Card, targeted follow up Checklist, appropriate warning in label and awareness among treating physicians.

Atypical femoral fractures: Other details – No statistical outputs are available.

Atypical femoral fractures	Details
Potential mechanisms	The mechanism(s) for the development of atypical fractures in patients taking bisphosphonates is not known. However, the main postulated mechanism is the suppression of bone turnover leading indirectly to ageing bone and the delay or prevention of repair of naturally occurring stress fractures although the evidence is not conclusive. The proposed mechanisms may also apply to the development of atypical fractures in association with bisphosphonates at sites other than the femur.
Evidence source(s) and strength of evidence	Based on the review of the available post-marketing data received in patients with multiple risk and confounding factors such as underlying metastatic bone lesions and/or osteoporosis, and concomitant medications (e.g. steroids and aromatase Inhibitors), there is insufficient evidence to establish a clear association between the occurrence of atypical fracture and the use of Zometa.
Characterization of the risk	The exact frequency is unknown. Atypical fractures normally require an invasive approach with hospitalization and surgery. A causal association with zoledronic acid is not clearly established.
Risk factors and risk groups	Possible risk factors for atypical femoral fractures include: - Long-term administration of bisphosphonate. - Underlying neoplastic disease such as advanced breast cancer, or multiple myeloma with bone lesions. - Concomitant therapies such as aromatase inhibitors, or glucocorticoids. - Radiotherapy at fracture site. Underlying metastatic bone lesions and/or osteoporosis.
Preventability	As stated in the SmPC Section 4.4, 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. Fractures are often bilateral; therefore, the contralateral femur should be examined in bisphosphonate-treated patients who have sustained a femoral shaft fracture. Discontinuation of bisphosphonate therapy in patients suspected to have

Atypical femoral fractures	Details
	an atypical femur fracture should be considered pending evaluation of the patient, based on an individual benefit risk assessment.
Impact on the benefit-risk balance of the product	Risk of atypical femur fracture is appropriately communicated through current labelling. No additional risk minimization measure is considered necessary. The analysis of review period data is consistent with previous cumulative analysis and did not provide any new relevant safety information pertaining to the important potential risk of atypical femur fracture. This safety concern has moderate impact on the benefit-risk balance of Zometa.
Public health impact	**Low.** The incidence of atypical femoral fractures in the overall population of Zometa-treated patients is uncommon and therefore, the potential public health impact is low. Moreover, a causal association with zoledronic acid is not clearly established.

Important potential risks

Teratogenicity: Other details – No statistical outputs are available.

Teratogenicity	Details
Potential mechanisms	The potential risk for human is unknown. In preclinical studies, bisphosphonates readily cross the placental barrier and are taken up into the developing foetal skeleton. Thus, the teratogenicity observed in the rat teratology study was attributed to the very potent action of the compound in lowering blood plasma calcium and binding to foetal bone with possible effects on cell function in general.

Teratogenicity	Details
Evidence source(s) and strength of evidence	Studies in animals with zoledronic acid have shown reproductive toxicological effects including malformations. Teratology studies were performed in two species, both via subcutaneous administration. Teratogenicity was observed in rats at doses ≥ 0.2 mg/kg and was manifested by external, visceral and skeletal malformations. No teratological or embryo/foetal effects were observed in rabbits, although maternal toxicity was marked at 0.1 mg/kg due to decreased serum calcium levels. There are no adequate and well-controlled studies of Zometa in pregnant women.
Characterization of the risk:	Animal reproduction studies with zoledronic acid have shown reproductive toxicity. There are no adequate data on the use of zoledronic acid in pregnant women. The potential risk for humans is unknown. Zometa should not be used during pregnancy. Women of child-bearing potential should be advised to avoid becoming pregnant.
Risk factors and risk groups	The potential risk for humans is unknown.
Preventability	Label recommend that Zometa should not be used during pregnancy. Women of child-bearing potential should be advised to avoid becoming pregnant.
Impact on the benefit-risk balance of the product	**Minimal.** With current label guidance the possibility of exposure in pregnant woman is considered low. No new safety information with 18 years of post-marketing experience.
Public health impact	**Low.** The risk is appropriately communicated in the label.

SVII.3.2. Presentation of the missing information

There is no missing information.

Part II: Module SVIII - Summary of the safety concerns

The important identified risks, important potential risks, and missing information for **Zometa** were established in the below table SVIII.1.

Table SVIII.1: Summary of safety concerns

List of important risks and missing information	
Important identified risks	• Osteonecrosis of the jaw • Atypical femoral fractures
Important potential risks	• Teratogenicity
Missing information	None

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

The MAH of the medicinal products **Zometa 4 mg powder and solvent for solution for infusion, Zometa 4 mg/5 ml concentrate for solution for infusion,** and **Zometa 4 mg/100 ml solution for infusion** have a Pharmacovigilance System in place to fulfil the legal requirements for pharmacovigilance contained in Directive 2001/83/EC and Regulation (EC) No 726/2004. The Pharmacovigilance System Master File (PSMF) describes the system and includes primary/minimum set of activities - routine pharmacovigilance.

The routine pharmacovigilance practices comply with the pharmacovigilance practices covered in the GVP and are suitable to identify and characterise the actual and potential new safety concerns of the medicinal product **Zometa 4 mg powder and solvent for solution for infusion, Zometa 4 mg/5 ml concentrate for solution for infusion,** and **Zometa 4 mg/100 ml solution for infusion.**

The routine pharmacovigilance activities focus on detection of adverse drug reactions and signal detection.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Yes.

Specific adverse reaction follow-up checklists:

Specific AE follow-up checklists will be used to collect further data to help further characterize and/or closely monitor each of the respective risks (Annex 4).

Other forms of routine pharmacovigilance activities

There are no other forms of routine PhV activities.

III.2 Additional pharmacovigilance activities

There are no ongoing additional pharmacovigilance activities for the **Zometa** products.

III.3 Summary Table of additional Pharmacovigilance activities

Table Part III.1: On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None.				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None.				
Category 3 - Required additional pharmacovigilance activities				
None.				

Part IV: Plans for post-authorisation efficacy studies

There is no post authorization development plan. There are no concerns about efficacy with **Zometa** and there is no data to suggest that previous efficacy evaluations with **Zometa** may need significant revision as related to the currently approved indications.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Important identified risks	
Osteonecrosis of the jaw	**Routine risk communication** SmPC Section 4.2, Section 4.4, Section 4.5, Section 4.8, and Package leaflet Section 2. **Routine risk minimization activities recommending specific clinical measures to address the risk:** A dental examination with appropriate preventive dentistry and an individual benefit-risk assessment is recommended prior to treatment with bisphosphonates in patients with concomitant risk factors. 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. **Other routine risk minimization measures beyond the Product Information:** None.

Safety concern	Routine risk minimization activities
Important identified risks	
Atypical femoral fractures	**Routine risk communication** SmPC Section 4.4, and Section 4.8. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Fractures are often bilateral; therefore, the contralateral femur should be examined in bisphosphonate-treated patients who have sustained a femoral shaft fracture. 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. **Other routine risk minimization measures beyond the Product Information:** None.
Important potential risks	
Teratogenicity	**Routine risk communication** SmPC Section 4.3, Section 4.6, Section 5.3, and Package leaflet Section 2. **Routine risk minimization activities recommending specific clinical measures to address the risk:** There are no adequate data on the use of zoledronic acid in pregnant women. Zometa should not be used during pregnancy. Women of child-bearing potential should be advised to avoid becoming pregnant. **Other routine risk minimization measures beyond the Product Information:** None.
Missing information	
None.	

V.2. Additional Risk Minimisation Measures

Patient reminder card

For the important identified risk of osteonecrosis of the jaw, the routine risk minimization activities are supplemented with an additional risk minimization measure: a patient reminder card (PRC).

Objectives:

To diagnose early and to initiate prompt treatment to minimize the risk of ONJ.

Rationale for the additional risk minimization activity:

The patient reminder card is distributed with the aim to inform patients and dentists that cases of ONJ are being reported with Zometa and possible measures to reduce the risk.

Target audience and planned distribution path:

Patients receiving Zometa therapy and dentists treating these patients for various dental conditions.

Plans to evaluate the effectiveness of the interventions and criteria for success:

The necessary information to assess the risk minimization measures will be obtained from the Phoenix Labs Safety Database and will include an assessment of the frequency and nature of reports of ONJ through spontaneous reporting.

The results of the monitoring of the risk minimization measures will be included in each periodic safety update report.

Outcome indicators: The effectiveness of the PRC on the risk for ONJ will be measured through monitoring and evaluating post market reporting rates of ONJ before and after introduction of the PRC and will also compare the EU reporting rate of ONJ post PRC introduction with the reporting rate of ONJ in the rest of the world. This evaluation will be performed with each Zometa PSUR. The content of the PRC will be reviewed with all labelling updates to ensure it contains the most relevant and up to date information.

Process Indicators: The MAH will monitor the extent of delivery of the PRC through existing Phoenix Labs tools and processes. The absolute number of PRCs distributed at the country level as agreed by national health authorities during the respective reporting period, will be presented in each PSUR.

V.3. Summary of risk minimisation measures

Summary of pharmacovigilance activities and risk minimization activities by safety concerns

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important identified risks		
Osteonecrosis of the jaw	**Routine risk minimisation measures:** Routine risk communication: *SmPC sections 4.2, 4.4, 4.5 and 4.8* *PL sections 2 and 4* Routine risk minimisation activities recommending specific clinical measures to address the risk: *recommendation for Osteonecrosis of the jaw monitoring is included in SmPC section 4.4.* Other routine risk minimisation measures: *Medicinal product subject only medical prescription intended for hospital use only, due to its pharmacological characteristics, its novelty, or for public health reasons* **Additional risk minimization measures:** Implementation of a Patient Reminder Card (PRC) for the patients receiving Zometa. Effectiveness is monitored in the PSUR.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted follow-up checklist. **Additional pharmacovigilance activities:** None.

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important identified risks		
Atypical femoral fractures	**Routine risk minimisation measures:** Routine risk communication: *SmPC sections 4.2, 4.4, 4.5 and 4.8* *PL sections 2 and 4* Routine risk minimisation activities recommending specific clinical measures to address the risk: *recommendation for Atypical femoral fractures monitoring is included in SmPC section 4.4.* Other routine risk minimisation measures: *Medicinal product subject only medical prescription intended for hospital use only, due to its pharmacological characteristics, its novelty, or for public health reasons* **Additional risk minimization measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted follow-up checklist. **Additional pharmacovigilance activities:** None.
Important potential risks		
Teratogenicity	**Routine risk minimisation measures:** Routine risk communication: *SmPC sections 4.2, 4.4, 4.5 and 4.8* *PL sections 2 and 4* **Additional risk minimization measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Missing information		
None.		

Part VI: Summary of the risk management plan

Summary of risk management plan for Zometa

This is a summary of the risk management plan (RMP) **Zometa**. The RMP details important risks **Zometa**, how these risks can be minimised, and how more information will be obtained about **Zometa** risks and uncertainties (missing information).

Zometa's summary of product characteristics (SmPC) and its package leaflet (PIL) give essential information to healthcare professionals and patients on how **Zometa** should be used.

This summary of the RMP for Zometa should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of **Zometa's** RMP.

I. The medicine and what it is used for

Zometa is authorized for:

- Prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumour-induced hypercalcemia) in adult patients with advanced malignancies involving bone.
- Treatment of adult patients with tumour-induced hypercalcemia (TIH).

Zometa contains zoledronic acid (powder and solvent for solution for infusion) as the active substance and is given by intravenous route of administration.

Further information about the evaluation of Zometa's benefits can be found in Zometa's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/zometa

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of **Zometa**, together with measures to minimize such risks and the proposed studies for learning more about **Zometa**'s risks, are outlined below.

In general, measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals.
- Important advice on the medicine's packaging.
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute **routine risk minimization measures**.

In the case of **Zometa**, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of important risks and missing information

Important risks of **Zometa** are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Zometa. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further

evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• Osteonecrosis of the jaw • Atypical femoral fractures
Important potential risks	• Teratogenicity
Missing information	• None

II.B Summary of important risks

Important identified risks

Osteonecrosis of the jaw	
Evidence for linking the risk to the medicine	Current evidence is based on the review of published literatures and post-marketing cases from safety database. The event is listed in the label.
Risk factors and risk groups	Osteonecrosis of the jaw has multiple risk factors including a diagnosis of cancer, concomitant therapies (e.g. chemotherapy, radiotherapy, corticosteroids) and co-morbid conditions (e.g. anaemia, coagulopathies, infection, pre-existing dental disease and poor oral cavity hygiene). Data suggest a greater frequency of reports of ONJ based on tumour type (advanced breast cancer, multiple myeloma).

Osteonecrosis of the jaw	
Risk minimisation measures	**Routine risk minimisation measures:** Routine risk communication: *SmPC sections 4.2, 4.4, 4.5 and 4.8* *PL sections 2 and 4* Routine risk minimisation activities recommending specific clinical measures to address the risk: *recommendation for Osteonecrosis of the jaw monitoring is included in SmPC section 4.4*. Other routine risk minimisation measures: *Medicinal product subject only medical prescription intended for hospital use only, due to its pharmacological characteristics, its novelty, or for public health reasons* **Additional risk minimization measures:** Implementation of a Patient Reminder Card (PRC) for the patients receiving Zometa. Effectiveness is monitored in the PSUR.

Atypical femoral fractures	
Evidence for linking the risk to the medicine	Based on the review of the available post-marketing data received in patients with multiple risk and confounding factors such as underlying metastatic bone lesions and/or osteoporosis, and concomitant medications (e.g. steroids and aromatase Inhibitors), there is insufficient evidence to establish a clear association between the occurrence of atypical fracture and the use of Zometa.
Risk factors and risk groups	Possible risk factors for atypical femoral fractures include - Long-term administration of bisphosphonate. - Underlying neoplastic disease such as advanced breast cancer, or multiple myeloma with bone lesions. - Concomitant therapies such as aromatase inhibitors, or glucocorticoids. - Radiotherapy at fracture site. Underlying metastatic bone lesions and/or osteoporosis.

Atypical femoral fractures	
Risk minimisation measures	**Routine risk minimisation measures:** Routine risk communication: *SmPC sections 4.2, 4.4, 4.5 and 4.8* *PL sections 2 and 4* Routine risk minimisation activities recommending specific clinical measures to address the risk: *recommendation for Atypical femoral fractures monitoring is included in SmPC section 4.4*. Other routine risk minimisation measures: *Medicinal product subject only medical prescription intended for hospital use only, due to its pharmacological characteristics, its novelty, or for public health reasons* **Additional risk minimization measures:** None.

Important potential risks

Teratogenicity	
Evidence for linking the risk to the medicine	Studies in animals with zoledronic acid have shown reproductive toxicological effects including malformations. Teratology studies were performed in two species, both via subcutaneous administration. Teratogenicity was observed in rats at doses ≥ 0.2 mg/kg and was manifested by external, visceral and skeletal malformations.
Risk factors and risk groups	The potential risk for humans is unknown.

Teratogenicity	
Risk minimisation measures	**Routine risk minimisation measures:** <u>Routine risk communication:</u> *SmPC sections 4.2, 4.4, 4.5 and 4.8* *PL sections 2 and 4* **Additional risk minimization measures:** None.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorization or specific obligation of **Zometa.**

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Zometa.

Annex 4 - Specific adverse drug reaction follow-up forms

This annex contains the specific adverse event targeted follow-up checklists used to collect additional data for the following Zometa RMP risks:

- Osteonecrosis of the Jaw;
- Atypical Femoral Fractures.

Bisphosphonate Osteonecrosis of the Jaw

Name of checklist (version/date): Bisphosphonate osteonecrosis of the jaw (ONJ) (version 6.0/Apr 2018).

Targeted Follow-Up
Checklist Bisphosphonate
Osteonecrosis of the jaw

ONJ is exposed bone in the oral cavity with no evidence of healing after 6 weeks of appropriate evaluation and dental care in the absence of metastatic disease in the jaw or osteoradionecrosis.

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed.

Has the patient previously received the Patient Reminder Card (PRC) on ONJ:

☐ Yes ☐ No ☐ Don't know

Did the patient have a dental examination with preventive dentistry prior to treatment with Zometa (Zoledronic acid)?

☐ Yes ☐ No ☐ Don't know

Information on Dose of suspected medication:

Drug name	Dose	Dosing regimen	Treatment date

Information on Dose of suspected medication:

Event	Diagnosis date	Dental treatment date	Event end date
ONJ			

Event Description:

Did the patient present with any of the following signs or symptoms? **Check all that apply**

☐ Area surrounding lesion red and/or swollen

☐ Swollen/tender lymph nodes on same side a lesion

☐ Suppuration (pus)

☐ Unable to eat

☐ Spontaneous pain

☐ Pain on palpation Unable to eat

☐ None of the above

Is bone exposed? ☐ Yes (please specify the largest dimension below) ☐ No ☐ Unknown

If Yes, largest dimension is ☐ <0.5 cm ☐ 0.5-0.99 cm ☐ 1.0-1.99 cm ☐>1.99 cm

NOTE: If bone is exposed, please contact the treating dentist / oral surgeon / periodontist to submit copies of the X-ray films/reports and dental notes describing the initial, follow-up and final presentations

Is the event accompanied by a bone/soft tissue infection?

☐ **Yes (*please specify including method of diagnosis (e.g. biopsy with isolated pathogen(s))*** ☐ No ☐ Unknown

Has the patient experienced complications of the reported event(s) (e.g. pathological fracture, fistula)?

☐ **Yes (please specify)** ☐ No ☐ Unknown

Was treatment given for the condition/symptoms?

☐ **Yes (please specify)** ☐ No ☐ Unknown

<u>Relevant medical history (concurrent and pre-existing conditions)</u>

(Please specify medical condition and date of onset)

Does the patient have a history of any of the following risk factors? ***Check all that apply and specify including dates***

☐ Cancer crowns, root canal

☐ Dental treatments (e.g. fillings, treatments, routine cleanings, deep scaling, orthodontics)

☐ Dental-surgical procedures (e.g. routine/surgical tooth extractions, periodontal surgery, implants) procedure

☐ Dental/oral problems (e.g. periodontal/ dental infections, toothache, stomatitis, oral ulcers)

☐ Treatment with corticosteroids

☐ Impaired healing after dental

☐ None of the above

☐ Poor oral hygiene

☐ Chemotherapy

☐ Radiotherapy to head and neck area

☐ Poor oral hygiene

☐ Trauma or fractures upper/lower

Previous use of bisphosphonates or other antiresorptive agents:

Has the patient taken any of the following drugs? ***Check all that apply and detail below***

☐ bisphosphonates ☐ other antiresorptive agents ☐ other

Drug	Route of administration	Dosing regimen or daily dose	Dates of treatment (dd/mm/yyyy)		Indication for use
			Start date	Stop date	

Bisphosphonate Atypical Femoral Fractures

Name of checklist (version/date): Bisphosphonate atypical femoral fractures (version 3.0/May 2018).

Targeted Follow-Up Checklist

Bisphosphonates

Atypical Femoral Fractures

This targeted follow-up checklist aims to collect major and minor features of atypical femoral fractures, as defined by the Task Force of the American Society of Bone and Mineral Research (Shane E *et al*., JBMR, 2014). In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed.

Is the femoral fracture located along the femoral diaphysis from just distal to the lesser trochanter to just proximal to the supracondylar flare?

☐ Yes ☐ No, the fracture is either above or below these limits ☐ Unknown

Major Features:

1) Was the fracture associated with no or minimal trauma (such as fall from standing height or less)?

☐ Yes ☐ No, the fracture was associated with a significant trauma ☐ Unknown

2) Does the fracture line originate at the lateral cortex and have a transverse or short-oblique configuration?

☐ Yes ☐ No, the fracture does not have transverse or short-oblique configuration (e.g. spiral fracture) ☐ Unknown

3) Is the fracture non-comminuted or minimally comminuted?

☐ Yes ☐ No, the fracture is comminuted ☐ Unknown

4) The fracture is: **a)** ☐ complete **b)** ☐ incomplete ☐ Unknown

4a) If the fracture is complete:

Does the fracture extend through both cortices?

☐ Yes ☐ No ☐ Unknown

Is the fracture associated with a medial spike?

☐ Yes ☐ No ☐ Unknown

4b) If the fracture is incomplete:

Does the fracture involve the lateral cortex?

☐ Yes ☐ No ☐ Unknown

5) Are there localized periosteal or endosteal thickening of the lateral cortex is present at the fracture site (e.g. breaking or flaring)

☐ Yes ☐ No, the fracture is comminuted ☐ Unknown

Supporting Information:

Please provide copies of all relevant source documents. (E.g., radiograph assessments, bone density results, operative notes, and pathology reports [e.g., histomorphometry analyses of iliac crest bone biopsies]).

Minor Features

1) Is there a generalized increase in the cortical thickness of the femoral diaphysis?

☐ Yes ☐ No ☐ Unknown

2) Were there unilateral or bilateral prodromal symptoms, such as dull or aching pain in the groin or thigh?

☐ Yes ☐ No ☐ Unknown

3) Were there bilateral incomplete or complete femoral diaphysis fractures?

☐ Yes ☐ No ☐ Unknown

4) Was there a delayed healing of the fracture?

☐ Yes ☐ No ☐ Unknown

5) Were there relevant co-morbid conditions?

a) Vitamin D deficiency ☐ Yes ☐ No ☐ Unknown

b) Rheumatoid arthritis ☐ Yes ☐ No ☐ Unknown

c) Hypophosphatasia ☐ Yes ☐ No ☐ Unknown

d) Other (please specify): _____

6) Did the patient take any of the following medications? Check all that apply:

☐ Glucocorticoids

☐ Proton pump inhibitors

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Prior to the launch of Zometa in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at to minimize the risk of developing ONJ while on Zometa therapy.

The MAH shall ensure that in each Member State where Zometa is marketed, all patients/carers who are expected to use Zometa have access to/are provided with the following educational message to be disseminated through professional bodies:

- Patient card.

Patient reminder card:

Phoenix Labs initiated osteonecrosis of the jaw (ONJ)-related risk minimization activities after ONJ was identified as a condition occurring predominantly in cancer patients treated with bisphosphonates. Based on the PRAC recommendation, Phoenix Labs will continue patient education by introduction and implementation of Patient Reminder Card (PRC) for the patients receiving Zometa.

Objective:

The objective is to minimize the risk of developing ONJ while on Zometa therapy.

Details of proposed patient reminder card Key

Safety Messages

- Inform doctor of oral problems before start of treatment
- Regular dental hygiene
- Side effects to be informed to doctor and dentist
- Risk factors for ONJ

Preventative measures

- Before the initiation of zoledronic acid:
  - Ask your doctor to provide information about ONJ
  - Check with your doctor, if dental examination is recommended
  - Inform your doctor/nurse of any problems in mouth or teeth
- During zoledronic acid therapy:
  - Maintain good oral hygiene, ensure proper fit of dentures and undergo routine dental check-ups
  - Inform doctor, if dental treatment (e.g. tooth extractions) is ongoing or planned.
  - Inform dentist regarding ongoing treatment with zoledronic acid
  - Inform doctor and dentist of signs of ONJ or any problems in mouth or teeth (e.g. loose teeth, pain or swelling, non-healing of sores or discharge)

Risk Factors

- Dental procedure (e.g. tooth extractions)
- Lack of routine dental care
- Gum disease
- Smoking
- Concomitant cancer treatment
- Previous treatment with bisphosphonate