NOVARTIS

Regulatory Affairs

Zoledronic Acid

Summary of the *EU* Safety Risk Management Plan

Active substance(s) (INN or common name):	*Zoledronic Acid*
Product(s) concerned (brand name(s)):	*Zometa*
Document status:	*Final*
Version number of the RMP Public Summary:	*13*
Date of final sign off of the RMP Public Summary	*06.12.2024*

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of “Zometa” is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the “Arzneimittelinformation / Information sur le médicament” approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of “Zometa” in Switzerland is the “Arzneimittelinformation/ Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic. Novartis Pharma Schweiz AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of “Zometa”.

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

Zometa's CDS 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 the Zometa 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 tumor-induced hypercalcemia) in adult patients with advanced malignancies involving bone;
- Treatment of adult patients with tumor-induced hypercalcemia (TIH).

Zometa contains zoledronic acid (powder and solvent for solution for infusion) as the active substance.

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 minimize or further characterize 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 CDS 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);

Table 13-1 List of important risks and missing information

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

Table 13-2 Important identified risk – 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. anemia, coagulopathies, infection, pre-existing dental disease and poor oral cavity hygiene). Data suggest a greater frequency of reports of ONJ based on tumor type (advanced breast cancer, multiple myeloma).
Risk minimization measures	**Routine risk minimization measures** CDS version 4.0 warnings and precautions **Additional risk minimization measures** Novartis has implemented Patient Reminder Card (PRC) for the patients receiving Zometa. Effectiveness is monitored in the PSUR.

Table 13-3 Important identified risk – 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.
Risk minimization measures	**Routine risk minimization measures** CDS version 4.0 warnings and precautions **Additional risk minimization measures** None.

II C: Post-authorization development planII.C.1 Studies which are conditions of the marketing authorization

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

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

There are no studies required for Zometa.