EU Risk Management Plan
for
Zoledronic Acid Accord 4 mg/5 ml concentrate for solution for infusion
Zoledronic Acid Accord 4 mg/100 ml solution for infusion
(Zoledronic Acid)

RMP version to be assessed as part of this application:

RMP Version number	7.1
Data lock point for this RMP	06-Jan-2025
Date of final sign off	21-Jan-2025

Rationale for submitting an updated RMP: This Risk management plan (RMP) has been updated as per the CHMP Type IB WS variation assessment report (EMA/VR/0000226953) for Zoledronic Acid Accord dated 30-Oct-2024.

Summary of significant changes in this RMP: Significant changes have been made in following sections of RMP: Part II (Module SVII), Part III, Part V, Part VI and Part VII (Annex 4, Annex 6, Annex 7 and Annex 8).

Other RMP versions under evaluation: Not Applicable

Details of the currently approved RMP:

Version	Approved with procedure	Date of approval
6.0	EMEA/H/C/002667/IB/0002	06-Nov-2015
3.0	PT/H/0742/001/II/010	13-Apr-2018

QPPV name: Dr. Arletta Werynska

QPPV signature: 

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Part I: Product(s) Overview

Table 1: Product Overview

Active substance(s) (INN or common name)	Zoledronic Acid
Pharmacotherapeutic group(s) (ATC Code)	**Pharmacotherapeutic group(s):** Drug affecting bone structure and mineralization, bisphosphonates **ATC code:** M05BA08
Marketing Authorisation Applicant	Accord Healthcare S.L.U., Spain,
Medicinal products to which this RMP refers	02
Invented name(s) in the European Economic Area (EEA)	Zoledronic Acid Accord 4 mg/5 ml concentrate for solution for infusion Zoledronic Acid Accord 4 mg/100 ml solution for infusion
Marketing authorisation procedure	Centralised Procedure: EMEA/H/C/002667 Decentralised Procedure: PT/H/0742/001/DC & PT/H/0742/001/E/001
Brief description of the product	Chemical class: Zoledronic acid belongs to the class of bisphosphonates and acts primarily on bone. It is an inhibitor of osteoclastic bone resorption.
	Summary of mode of action: The selective action of bisphosphonates on bone is based on their high affinity for mineralised bone, but the precise molecular mechanism leading to the inhibition of osteoclastic activity is still unclear. In long-term animal studies, zoledronic acid inhibits

	bone resorption without adversely affecting the formation, mineralization or mechanical properties of bone. In addition to being a potent inhibitor of bone resorption, zoledronic acid also possesses several anti-tumour properties that could contribute to its overall efficacy in the treatment of metastatic bone disease.
	Important information about its composition: Zoledronic Acid Accord 4 mg/5 ml concentrate for solution for infusion One vial with 5 ml concentrate contains 4 mg zoledronic acid (as monohydrate) One ml concentrate contains 0.8 mg zoledronic acid (as monohydrate). Zoledronic acid Accord 4 mg/100 ml solution for infusion Each bag with 100 ml solution contains 4 mg zoledronic acid. One ml solution contains 0.04 mg zoledronic acid. *Excipient with known effect* Each bag with 100 ml solution contains 342.9 mg (14.9 mmol) of sodium
Hyperlink to the Product Information	Refer Module 1.3.1 for Product Information
Indication(s) in the EEA	*Current* • Prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumour-induced hypercalcaemia) in adult patients with advanced malignancies involving bone. • Treatment of adult patients with tumour-induced hypercalcaemia (TIH).

Dosage in the EEA	*Current* **<u>Posology:</u>** Zoledronic Acid must only be prescribed and administered to patients by healthcare professionals experienced in the administration of intravenous bisphosphonates. <u>Prevention of skeletal related events in patients with advanced malignancies involving bone</u> *Adults and elderly* The recommended dose in the prevention of skeletal related events in patients with advanced malignancies involving bone is 4 mg zoledronic acid every 3 to 4 weeks. Patients should also be for administered an oral calcium supplement of 500 mg and 400 IU vitamin D daily. The decision to treat patients with bone metastases the prevention of skeletal related events should consider that the onset of treatment effect is 2-3 months. <u>Treatment of TIH</u> *Adults and elderly* The recommended dose in hypercalcaemia (albumin-corrected serum calcium ≥12.0 mg/dl or 3.0 mmol/l) is a single dose of 4 mg zoledronic acid. **Method of administration** Intravenous use.
Pharmaceutical form(s) and strengths	*Current* Solution for infusion 4 mg/5 ml and 4 mg/100 ml

Is the product subject to additional monitoring in the EU?	No

Part II: Safety specification

Module SI - Epidemiology of the indication(s) and target population(s)

Not applicable

Module SII - Non-clinical part of the safety specification

Not applicable

Module SIII - Clinical trial exposure

Not applicable

Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Not applicable

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

Not applicable

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Not applicable

Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

Not applicable

Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Not applicable - there is no potential for misuse for illegal purposes.

Module SVII - Identified and potential risks

Not applicable

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

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable

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

Not applicable

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

Not applicable

SVII.3.2 Presentation of the missing information

Not Applicable

Module SVIII - Summary of the safety concerns

Table 2: Summary of safety concerns

Important identified risks	• Osteonecrosis of the jaw (ONJ) • Atypical femur fractures
Important potential risks	• Teratogenicity
Missing information	• None

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

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for following risk concerning use of zoledronic acid:

Important identified risks

- Osteonecrosis of the jaw (ONJ)
- Atypical femoral fractures

Purpose: For collection and reporting of safety information while use of zoledronic acid.

Targeted follow-up questionnaires are appended in Annex 4 of this RMP.

III.2 Additional pharmacovigilance activities

None proposed.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable.

Part IV: Plans for post-authorisation efficacy studies

Not applicable

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

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table 3: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important Identified Risks	
Osteonecrosis of the jaw (ONJ)	Routine risk communication: • SmPC Sections: 4.4 and 4.8 • PIL Section: 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk*: SmPC section 4.4 mentions that: • Treatment should be delayed in patients with unhealed open soft tissue lesions in the mouth, except in medical emergency situations. • A dental examination with appropriate preventive dentistry and an individual benefit-risk assessment is recommended prior to treatment in patients with concomitant risk factors. • All patients should be encouraged to maintain good oral hygiene, undergo routine dental check-ups and immediately report any oral symptoms during treatment. Other routine risk minimisation measures beyond the Product Information: Legal status:

Safety concern	**Routine risk minimisation activities**
	• Prescription only status of the product.
Atypical femur fractures	Routine risk communication: • SmPC Sections: 4.4 and 4.8 • PIL Section: 4 *Routine risk minimisation activities recommending specific clinical measures to address the risk*: SmPC section 4.4 mentions that: • Discontinuation of 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. • During 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. Other routine risk minimisation measures beyond the Product Information: Legal status: • Prescription only status of the product.

Safety concern	**Routine risk minimisation activities**
Important Potential Risks	
Teratogenicity	Routine risk communication: • SmPC Section: 4.6 • PIL Section: 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk*: • Zoledronic acid is not recommended in women of childbearing potential is mentioned in SmPC section 4.6. Other routine risk minimisation measures beyond the Product Information: Legal status: • Prescription only status of the product.

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) is part of the patient information pack.

Objectives:

To minimize the risk of ONJ as much as possible, by further extending the awareness to the patient.

Rationale for the additional risk minimization activity:

Since Zoledronic acid is being administered once a year, the patient should have adequate information available, so that they can prevent the occurrence of ONJ by taking appropriate measures/precautions.

Target audience and planned distribution path:

Patient reminder cards will be distributed locally to physicians for dissemination to patients receiving Zoledronic acid.

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

Routine pharmacovigilance activities involving analysis of ADR reports to assess compliance with SmPC recommendations will allow assessing and judging the success of the risk minimisation measures. Effectiveness of this measure will be analysed by MAH as per the requirements for submission of periodic safety update reports (PSUR) for this medicinal product as per local country specific requirement or as set out in the list of European Union Reference Dates (EURD list) provided as per Article 107c (7) of Directive 2001/83/EC and any subsequent updates published on the European Medicines Agency's web-portal and also will be evaluated in details in periodic signal management activity.

V.3 Summary of risk minimisation measures

Safety concern	Routine risk minimisation measures	Pharmacovigilance activities
Important identified risks		

Safety concern	Routine risk minimisation measures	Pharmacovigilance activities
Osteonecrosis of Jaw	**Routine risk minimization measures** • SmPC sections 4.4 and 4.8 • PL Section 2 • SmPC section 4.4 mentions that: o Treatment should be delayed in patients with unhealed open soft tissue lesions in the mouth, except in medical emergency situations. o 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. o All patients should be encouraged to maintain good oral hygiene, undergo routine dental check-ups and immediately report any oral symptoms during treatment. • Prescription only status of the product **Additional risk minimization measures** • Patient Reminder Card	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Targeted follow-up questionnaire **Additional pharmacovigilance activities:** None

Safety concern	Routine risk minimisation measures	Pharmacovigilance activities
Atypical femur fractures	**Routine risk minimization measures** • SmPC sections 4.4 and 4.8 • PL Section 4 • SmPC section 4.4 mentions that: o Discontinuation of 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. o During 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. • Prescription only status of the product **Additional risk minimization measures** • None	**<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u>** • Targeted follow-up questionnaire **Additional pharmacovigilance activities:** None

Safety concern	Routine risk minimisation measures	Pharmacovigilance activities
Important potential risks		
Teratogenicity	**Routine risk minimization measures** • SmPC section 4.6 • PL Section 2 • Zoledronic acid is not recommended in women of childbearing potential is mentioned in SmPC section 4.6. • Prescription only status of the product **Additional risk minimization measures** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Part VI: Summary of the risk management plan

Summary of risk management plan for Zoledronic Acid Accord 4 mg/5 ml concentrate for solution for infusion and Zoledronic Acid Accord 4 mg/100 ml solution for infusion (Zoledronic acid).

This is a summary of the risk management plan (RMP) for Zoledronic Acid Accord 4 mg/5 ml concentrate for solution for infusion and Zoledronic Acid Accord 4 mg/100 ml solution for infusion. The RMP details important risks of Zoledronic Acid Accord, how these risks can be minimised, and how more information will be obtained for Zoledronic Acid Accord's risks and uncertainties (missing information).

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

This summary of the RMP for Zoledronic Acid Accord 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 Zoledronic Acid Accord's RMP.

I. The medicine and what it is used for

Zoledronic Acid Accord is indicated in adults for the treatment of:

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

It contains Zoledronic Acid as the active substance and it is given by intravenous route.

Further information about the evaluation of Zoledronic Acid Accord's benefits can be found in Zoledronic Acid Accord'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/zoledronic-acid-accord.

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

Important risks of Zoledronic Acid Accord, together with measures to minimise such risks and and the proposed studies for learning more about Zoledronic Acid Accord's risks, are outlined below.

Measures to minimise 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 minimise its risks.

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

In the case of Zoledronic Acid Accord these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, 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 Zoledronic Acid Accord are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. 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 Zoledronic Acid Accord. 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):

Important identified risks	• Osteonecrosis of the jaw (ONJ) • Atypical femur fractures
Important potential risks	• Teratogenicity
Missing information	• None

II.B Summary of important risks

Important Identified Risk: Osteonecrosis of Jaw	
Risk minimisation measures	<u>Routine risk minimisation measures:</u> • SmPC sections 4.4 and 4.8 • PL Section 2 • SmPC section 4.4 mentions that: o Treatment should be delayed in patients with unhealed open soft tissue lesions in the mouth, except in medical emergency situations. o 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. o All patients should be encouraged to maintain good oral hygiene, undergo routine dental check-ups and immediately report any oral symptoms during treatment with. <u>Additional risk minimisation measures:</u> • Patient Reminder Card

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 authorisation or specific obligation of Zoledronic Acid Accord.

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

There are no studies required for Zoledronic Acid Accord.

Annex 4 - Specific adverse drug reaction follow-up forms

MAH has developed the follow-up questionnaires for the following safety concerns:

- Osteonecrosis of the jaw (ONJ)
- Atypical femur fractures

Targeted Follow-up Questionnaire

Osteonecrosis of the Jaw (ONJ)

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

(This question is applicable for Zoledronic Acid Accord and EU/EEA countries ONLY)

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

☐ Yes ☐ No ☐ Don't know

Information on Dose of suspected medication:

Drug name	Dose	Dosing regimen	Treatment date

Information on event duration:

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

☐ Suppuration (pus)

☐ Spontaneous pain

☐ Swollen/tender lymph nodes on same side as lesion

☐ Pain on palpation

☐ Unable to eat

☐ None of the above

Where was the jaw location of the observed lesion? *(Please include the overall size)*

☐ Upper left ☐ Lower left
☐ Upper front ☐ Lower front
☐ Upper right ☐ Lower right

Length(cm)	Width (cm)

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**

Relevant medical history (concurrent and pre-existing conditions)
(*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
☐ Chemotherapy
☐ Radiotherapy to head and neck area
☐ Treatment with corticosteroids
☐ Poor oral hygiene
☐ None of the above
☐ Dental treatments (e.g. fillings, crowns, root canal, treatments, routine cleanings, deep scaling orthodontics)
☐ Dental-surgical procedures (e.g.routine/surgical tooth extractions, periodontal surgery, implants)
☐ Impaired healing after dental procedure
☐ Trauma or fractures upper/lower Jaw
☐ Dental/oral problems (e.g. periodontal/dental infections, toothache, stomatitis, oral ulcers)

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

[redacted]

List details for the above drugs as appropriate

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

Targeted Follow-up Questionnaire

Atypical Femur Fractures

This targeted follow-up questionnaire aims to collect major and minor features of atypical femur 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 femur 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, the fracture involves only the medial cortex ☐ Unknown

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

☐ Yes ☐ No ☐ 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., histomorphometric 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

Prior to use of Zoledronic acid Accord in each Member State, the MAH must agree the content and format of the Patient Reminder Card, including communication media, distribution modalities, and any other aspects of the programme, with the national competent authority (NCA).

The MAH shall ensure that in each Member State where Zoledronic acid Accord is marketed, all patients/carers who are expected to use Zoledronic acid Accord are provided with the following educational material:

- Patient reminder card

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