EU RISK MANAGEMENT PLAN FOR

ZERLINDA and ZOLEDRONIC ACID TEVA (ZOLEDRONIC ACID)

RMP version to be assessed as part of this application	
RMP version number	9.2
Data lock point for this RMP	30 November 2025
Date of final sign off	08 April 2026
Rationale for submitting an updated RMP	Alignment of list of safety concerns and follow-up questionnaires (FUQs) with the reference product's (Zometa, Phoenix labs) RMP v12.2, published on EMA website on 11 August 2025.

QPPV Details	
QPPV name:	Iva Novak
QPPV signature:	The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV/deputy. The electronic signature is available on file.

Table 1: Summary of Significant Changes in This RMP Version

RMP part/module	Part/module version number and date of approval (opinion date)	High level description of major changes
Part I Product(s) overview	SE/H/2325/001/DC: 9.0 (13 February 2019) EMEA/H/C/002439: 6.0 (06 October 2017)	Administrative updates to jointly present information from all EU procedures encompassed by the RMP. Section revised to present data according to the GVP Module V revision 2.0.1 RMP template requirements.
Part II - Module SI Epidemiology of the indication(s) and target population(s)	SE/H/2325/001/DC: 9.0 (13 February 2019) EMEA/H/C/002439: 6.0 (06 October 2017)	Not applicable.
Part II - Module SII Non-clinical part of the safety specification	SE/H/2325/001/DC: 9.0 (13 February 2019) EMEA/H/C/002439: 6.0 (06 October 2017)	Not applicable.
Part II - Module SIII Clinical trial exposure	SE/H/2325/001/DC: 9.0 (13 February 2019) EMEA/H/C/002439: 6.0 (06 October 2017)	Not applicable.
Part II - Module SIV Populations not studied in clinical trials	SE/H/2325/001/DC: 9.0 (13 February 2019) EMEA/H/C/002439: 6.0 (06 October 2017)	Not applicable.
Part II - Module SV Post-authorisation experience	SE/H/2325/001/DC: 9.0 (13 February 2019) EMEA/H/C/002439: 6.0 (06 October 2017)	The section was updated to not applicable according to GVP Module V revision 2.0.1 RMP template requirements.
Part II - Module SVI Additional EU requirements for the safety specification	SE/H/2325/001/DC: 9.0 (13 February 2019)	Not applicable.

RMP part/module	Part/module version number and date of approval (opinion date)	High level description of major changes
	EMEA/H/C/002439: 6.0 (06 October 2017)	
Part II - Module SVII Identified and potential risks	SE/H/2325/001/DC: 9.0 (13 February 2019) EMEA/H/C/002439: 6.0 (06 October 2017)	List of safety concerns updated in line with the reference product's (Zometa, Phoenix labs) RMP v12.2.
Part II - Module SVIII Summary of the safety concerns	SE/H/2325/001/DC: 9.0 (13 February 2019) EMEA/H/C/002439: 6.0 (06 October 2017)	List of safety concerns updated in line with the reference product's (Zometa, Phoenix labs) RMP v12.2
Part III Pharmacovigilance plan (including post-authorisation safety studies)	SE/H/2325/001/DC: 9.0 (13 February 2019) EMEA/H/C/002439: 6.0 (06 October 2017)	Section revised to present data according to the GVP Module V revision 2.0.1 RMP template requirements and to reflect changes introduced to the list of safety concerns. Follow-up questionnaire (FUQ) for risk of 'Osteonecrosis of the jaw (ONJ)' added.
Part IV Plans for post-authorisation efficacy studies	SE/H/2325/001/DC: 9.0 (13 February 2019) EMEA/H/C/002439: 6.0 (06 October 2017)	Not applicable.
Part V Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)	SE/H/2325/001/DC: 9.0 (13 February 2019) EMEA/H/C/002439: 6.0 (06 October 2017)	Section revised to present data according to the GVP Module V revision 2.0.1 RMP template requirements and to align with Part II, module SVIII.
Part VI Summary of the risk management plan	SE/H/2325/001/DC: 9.0 (13 February 2019) EMEA/H/C/002439: 6.0 (06 October 2017)	Alignment with Part II, module SVIII. Separate Part VI provided for each EU procedure.

RMP part/module	Part/module version number and date of approval (opinion date)	High level description of major changes
Part VII Annexes	SE/H/2325/001/DC: 9.0 (13 February 2019) EMEA/H/C/002439: 6.0 (06 October 2017)	Section revised to present data according to the GVP Module V revision 2.0.1 RMP template requirements. Annex 4: FUQs updated to align with FUQs from the reference product Zometa (Phoenix labs) RMP v12.2, and with Teva questionnaire template. Annex 8: Summary of Changes to the Risk Management Plan over Time updated.

Details of the currently approved RMP		
Version number	9.0	6.0
Approved with procedure	SE/H/2325/001/ (former DK/H/2265/001/DC)	EMEA/H/C/002439
Date of approval (opinion date)	13 February 2019	06 October 2017

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
ARMM	Additional Risk Minimisation Measure
ATC	Anatomical Therapeutic Chemical
CTD	Common Technical Document
DDD	Defined Daily Dose
EEA	European Economic Area
e.g.	example given
EMA	European Medicines Agency
EU	European Union
i.e.	Id est (engl.: that means)
INN	International Non-proprietary Name
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
ONJ	Osteonecrosis of the Jaw
PIL	Patient Information Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PT	Preferred Term
QPPV	Qualified Person Responsible for Pharmacovigilance
RMP	Risk Management Plan
SPC, SmPC	Summary Of Product Characteristics
TIH	Tumour-induced Hypocalcaemia
WHO	World Health Organisation

Part I: Product(s) Overview

Table 2: Product Overview

Active substance(s) (INN or common name)	**Zoledronic acid**
Pharmacotherapeutic group(s) (ATC Code)	Drugs for treatment of bone diseases; Bisphosphonates (M05BA08)
Marketing Authorisation Holder	SE/H/2325/001/DC: Actavis Group PTC ehf. EMEA/H/C/002439: TEVA B.V.
Medicinal products to which this RMP refers	2
Invented name(s) in the European Economic Area (EEA)	Zerlinda (SE/H/2325/001/DC) Zoledronic Acid Teva (EMEA/H/C/002439)
Marketing authorisation procedure	Decentralised (SE/H/2325/001/DC) Centralised (EMEA/H/C/002439)
Brief description of the product	**Chemical class**: Bisphosphonates
	Summary of mode of action: Zoledronic acid belongs to the class of bisphosphonates and 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 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, mineralisation 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. The following properties have been demonstrated in preclinical studies: *In vivo:* Inhibition of osteoclastic bone resorption, which alters the bone marrow microenvironment, making it less conducive to tumour cell growth and anti-angiogenic 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.
	Important information about its composition: Not applicable.

Hyperlink to the Product Information	Please refer to CTD Module 1.3.1.
Indication(s) in the EEA	**Current (if applicable)**: 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).
	Proposed (if applicable): Not applicable.
Dosage in the EEA	**Current (if applicable)**: *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 zoledronic acid every 3 to 4 weeks. *Treatment of TIH:* 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.
	Proposed (if applicable): Not applicable.
Pharmaceutical form(s) and strengths	**Current (if applicable)**: 4 mg/100 ml, solution for infusion (SE/H/2325/001/DC) 4 mg/5 ml, concentrate for solution for infusion (EMEA/H/C/002439)
	Proposed (if applicable): 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)

Not applicable.

Part II: Module SII - Non-Clinical Part of the Safety Specification

Not applicable.

Part II: Module SIII - Clinical Trial Exposure

Not applicable.

Part II: Module SIV - Populations Not Studied in Clinical Trials

Not applicable.

Part II: Module SV - Post-Authorisation Experience

Not applicable.

Part II: Module SVI - Additional EU Requirements for the Safety Specification

Not applicable.

Part II: Module SVII - Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

The safety concerns in the initially approved zoledronic acid EU RMP v1.0 were defined as follows:

Table 3: Safety Concerns in Zoledronic acid EU RMP v1.0

List of important risks and missing information	
Important identified risks	• Osteonecrosis of the jaw (ONJ) • Hypocalcaemia • Renal function impairment • Acute phase reaction • Hypersensitivity reactions • Ocular adverse events • Atrial fibrillation
Important potential risks	• Atypical femoral fractures • Cardiac arrhythmias • Fracture healing impairment • Cerebrovascular adverse events • Focal segmental glomerulosclerosis • Interstitial lung disease • Potential interaction with nephrotoxic drugs • Medication errors
Missing information	• Use in races other than Caucasians • Use during pregnancy and lactation • Use in patients below 18 years of age • Use in patients with severe renal impairment • Use in patients with severe hepatic insufficiency

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Reasons for the reclassification, removal and addition to the list of safety concerns in RMP v9.2:

The list of safety concerns has been aligned with the reference medicinal product's (Zometa, MAH: Phoenix labs) RMP v12.2, published on EMA website on 11 August 2025.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

Not applicable.

Part II: Module SVIII - Summary of the Safety Concerns

Table 4: Summary of Safety Concerns

List of important risks and missing information	
Important identified risks	• Osteonecrosis of the jaw (ONJ) • Atypical femoral 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 are considered sufficient to monitor the benefit-risk profile of the product and to detect any safety concerns.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires:

Follow-up questionnaires will be sent only to the stakeholders who have the knowledge/background to provide the information as requested in the questionnaire.

Table 5: List of Questionnaires

Questionnaire/purpose	Trigger events*
Osteonecrosis of the jaw (ONJ) To follow-up and collect in more details information to further characterise safety concerns and evaluate risk factors.	MedDRA PTs: Osteonecrosis of jaw, Osteonecrosis
Atypical femoral fractures To follow-up and collect in more details information to further characterise safety concerns and evaluate risk factors.	MedDRA PTs: Atypical femur fracture and Femur fracture

*List of trigger terms is displayed according to MedDRA version 28.1 and will be updated with MedDRA version upgrades as needed to accommodate any relevant changes.

Other forms of routine pharmacovigilance activities:

Not applicable.

III.2 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 6: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation measures
Osteonecrosis of the jaw (ONJ)	**Routine risk communication:** Risk is addressed in SmPC section 4.4, 4.5 and 4.8. Described in PL sections 2 and 4. **Routine risk minimisation measures recommending specific clinical measures to address the risk:** None. **Other routine risk minimisation measures beyond the Product Information:** Legal status: Prescription only medicine.
Atypical femoral fractures	**Routine risk communication:** Risk is addressed in SmPC sections 4.4 and 4.8. Described in PL section 4. **Routine risk minimisation measures recommending specific clinical measures to address the risk:** None. **Other routine risk minimisation measures beyond the Product Information:** Legal status: Prescription only medicine.
Teratogenicity	**Routine risk communication:** Risk is addressed in SmPC section 5.3 **Routine risk minimisation measures recommending specific clinical measures to address the risk:** None. **Other routine risk minimisation measures beyond the Product Information:** Legal status: Prescription only medicine.

V.2. Additional Risk Minimisation Measures

Table 7: Patient Card for Risk of ONJ

Objectives	**To diagnose early and to initiate prompt treatment to minimise the risk of ONJ**
Rationale for the additional risk minimisation activity	Patient card contains important safety information for patients in order to be aware of the risk of osteonecrosis of the jaw before and during treatment with zoledronic acid.
Target audience and planned distribution path	Patient card will be distributed in accordance with the distribution plan agreed with national agencies. The MAH will track the extent of patient card distribution.
Plans to evaluate the effectiveness of the interventions and criteria for success	The success of proposed additional risk minimization activities will be measured by: • monitoring the success of risk minimization tool implementation per country. The implementation will be considered successful if MAH fulfilled obligation(s). • potential increase in the relevant cases. The ARMMs will be considered successful if no significant increase in the period after ARMMs implementation compared to previous period, without an alternative explanation, is noticed. Results of effectiveness evaluation will be presented in periodic reports.

V.3. Summary of Risk Minimisation Measures

Table 8: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Osteonecrosis of the jaw (ONJ)	**Routine risk minimisation measures:** SmPC sections 4.4, 4.5 and 4.8. PL sections 2 and 4. Prescription only medicine. **Additional risk minimisation measures:** Patient card.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** AE follow-up form for adverse reactions. **Additional pharmacovigilance activities:** None.
Atypical femoral fractures	**Routine risk minimisation measures:** SmPC sections 4.4, and 4.8. PL section 4. Prescription only medicine. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** AE follow-up form for adverse reactions. **Additional pharmacovigilance activities:** None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Teratogenicity	**Routine risk minimisation measures:** SmPC section 5.3. Prescription only medicine. **Additional risk minimisation 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 ZERLINDA (ZOLEDRONIC ACID)

This is a summary of the risk management plan (RMP) for Zerlinda (hereinafter referred to as Zoledronic acid). The RMP details important risks of Zoledronic acid, how these risks can be minimised, and how more information will be obtained about Zoledronic acid's risks and uncertainties (missing information).

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

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

I. The Medicine and What It is used for

Zoledronic acid is authorised for prevention of skeletal related events in patients with advanced malignancies involving bone, and tumour-induced hypocalcaemia (see SmPC for the full indication). It contains zoledronic acid as the active substance and it is given intravenously.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Zoledronic acid, together with measures to minimise such risks and the proposed studies for learning more about Zoledronic acid'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, these measures are supplemented with additional risk minimisation measure mentioned under relevant important risk, 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 are risks that need special risk management activities to further investigate or minimise 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 Zoledronic acid. 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 (ONJ) • Atypical femoral fractures
Important potential risks	• Teratogenicity
Missing information	• None

II.B Summary of Important Risks

Table 9: Summary of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Important potential risk: Osteonecrosis of the jaw (ONJ)	
Risk minimisation measures	**Routine risk minimisation measures** SmPC sections 4.4, 4.5 and 4.8. PL sections 2 and 4. Prescription only medicine. **Additional risk minimisation measures** Patient 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.

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for Zoledronic acid.

Summary of Risk Management Plan for ZOLEDRONIC ACID TEVA (ZOLEDRONIC ACID)

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

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

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

I. The Medicine and What It is used for

Zoledronic Acid Teva is authorised for prevention of skeletal related events in patients with advanced malignancies involving bone, and tumour-induced hypocalcaemia (see SmPC for the full indication). It contains zoledronic acid as the active substance and it is given intravenously.

Further information about the evaluation of Zoledronic Acid Teva's benefits can be found in Zoledronic Acid Teva's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: Zoledronic acid Teva | European Medicines Agency (EMA).

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Zoledronic Acid Teva, together with measures to minimise such risks and the proposed studies for learning more about Zoledronic Acid Teva'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 Teva, these measures are supplemented with additional risk minimisation measure mentioned under relevant important risk, 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 Teva are risks that need special risk management activities to further investigate or minimise 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 Zoledronic Acid Teva. 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 (ONJ) • Atypical femoral fractures
Important potential risks	• Teratogenicity
Missing information	• None

II.B Summary of Important Risks

Table 10: Summary of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Important potential risk: Osteonecrosis of the jaw (ONJ)	
Risk minimisation measures	**Routine risk minimisation measures** SmPC sections 4.4, 4.5 and 4.8. PL sections 2 and 4. Prescription only medicine. **Additional risk minimisation measures** Patient 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 Teva.

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for Zoledronic acid Teva.

Part VII: ANNEXES

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Annex 4 – Specific Adverse Drug Reaction Follow-Up Forms

Follow-up forms:

- Atypical femoral fracture – follow-up questionnaire v2.1
- Osteonecrosis of the jaw (ONJ) – follow-up questionnaire v1.0

Zoledronic acid – Atypical femoral fracture

- Supplement to the (S)AE Form -

You have received this questionnaire because you have reported Atypical femoral fracture with Teva's medicinal product. Please provide additional information below, if available to you. By providing this information, you are actively participating in safety monitoring of medicinal product's use.

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.

Follow-up to Case No.: .....

Date of receipt (dd/mm/yyyy): .....

PATIENT INFORMATION:

Age: .....

Gender: ..... Pregnant: .....

Height: ..... Weight: .....

REPORTED DRUG INFORMATION

Product: .....

Batch number: ..... Exp. date (mm/yy): .....

Indication for which Zoledronic acid was used: .....

.....

.....

Zoledronic acid route of administration: ..... Zoledronic acid posology: .....

Therapy start date (dd/mm/yy): ..... Therapy end date (dd/mm/yy): .....

.....

Or if the date is not available/not relevant:

Duration of Zoledronic acid therapy: .....

Exposure to Zoledronic acid at the time the adverse event occurred (if therapy dates unknown):
☐ Yes ☐ No

Dates of any previous Zoledronic acid exposure (dd/mm/yy): .....

Action taken with Zoledronic acid:

☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug withdrawn

- Has there been any improvement after stopping Zoledronic acid?
  ☐ Yes ☐ No ☐ Not applicable

- Did the adverse event reappear after reintroduction of Zoledronic acid?
  ☐ Yes ☐ No ☐ Not applicable

ADVERSE EVENT DATA

Reported event:.....

Event onset date (dd/mm/yy):..... Event end date (dd/mm/yy):.....

.....

Time to event onset after initiating the Zoledronic acid treatment:.....

List specific details (clinical presentation (incl. signs and symptoms), clinical findings, and precise sequence of events:.....

.....

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:

   ☐ Complete ☐ 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

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

Adverse event **treatment**: .....

.....

Event outcome

If recovered/ resolved, please specify the time from onset of symptoms until recovery (in days):

.....

If recovered with sequelae/ not resolved, please specify details:.....

.....

.....

MEDICAL HISTORY/ ADDITIONAL DETAILS

Patient history

Does the patient have any relevant (past/ concomitant) medical history?

☐ Yes ☐ No

If yes, please specify:.....

.....

Concomitant drugs

Did the patient take any relevant concomitant medications? ☐ Yes ☐ No

If yes, please provide the following information for each concomitant medication used in the patient's treatment:

Product Name (and active substance)	**Route of admin.**	**Posology** (dose; e.g. mg/kg, mcg)	**Drug Start Date** (dd/mm/ yy)	**Drug Stop Date** (dd/mm / yy)	**Indication**	**Causal relationship with event?** (Yes/No)

Relevant laboratory/ diagnostic tests data

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]).

Test	**Date** (dd/mm/yy)	**Result**

REPORTER INFORMATION:

☐ Physician; ☐ Patient; ☐ Other, please specify .....

.....

Name and title: .....

.....

Affiliation: .....

.....

Address: .....

.....

Phone number: ..... E-mail: .....

.....

Date of report (dd/mm/yy): .....

Signature: .....

FURTHER INFORMATION (if applicable)

Contact details of the specialist to whom the patient was referred for further evaluation of the reported event(s):

Name: .....

Address: .....

Phone number: .....

Zoledronic acid – Osteonecrosis of the jaw (ONJ)

- Supplement to the (S)AE Form -

You have received this questionnaire because you have reported Osteonecrosis of the jaw with Teva's medicinal product. Please provide additional information below, if available to you. By providing this information, you are actively participating in safety monitoring of medicinal product's use.

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.

Follow-up to Case No.:.....

Date of receipt (dd/mm/yyyy):.....

PATIENT INFORMATION:

Age:.....

Gender: ..... Pregnant: .....

Height: ..... Weight:.....

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

☐ Yes ☐ No ☐ Unknown

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

☐ Yes ☐ No ☐ Unknown

REPORTED DRUG INFORMATION

Information on Dose of suspected medication:

Drug name	Dose	Dosing regimen	Treatment date

Action taken with Zoledronic acid:

☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug withdrawn

- Has there been any improvement after stopping Zoledronic acid?
  ☐ Yes ☐ No ☐ Not applicable

- Did the adverse event reappear after reintroduction of Zoledronic acid?
  ☐ Yes ☐ No ☐ Not applicable

ADVERSE EVENT DATA

Information on Dose of suspected medication:

Event	Diagnosis date	Dental treatment date	Event end date
ONJ			

List specific details (clinical presentation (incl. signs and symptoms), clinical findings, and precise sequence of events:.....

.....

Event outcome

If recovered/ resolved, please specify the time from onset of symptoms until recovery (in days):

.....

If recovered with sequelae/ not resolved, please specify details:.....

.....

.....

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

☐ 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 Xray 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

MEDICAL HISTORY/ ADDITIONAL DETAILS

REPORTER INFORMATION (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 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

☐ Poor oral hygiene

☐ Chemotherapy

☐ Radiotherapy to head and neck area

☐ Trauma or fractures upper/lower

☐ None of the above

Concomitant drugs:

PREVIOUS USE OF BISPOSPHONATES OR OTHER ANTIRESORPPTIVE 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	

Relevant laboratory/ diagnostic tests data (Please forward any relevant documents or reports.)

Test	Date (dd/mm/yy)	Result

REPORTER INFORMATION:

☐ Physician; ☐ Patient; ☐ Other, please specify.....

.....

Name and title:.....

.....

Affiliation:.....

.....

Address:.....

.....

Phone number:..... E-mail:.....

.....

Date of report (dd/mm/yy):.....

Signature: .....

FURTHER INFORMATION (if applicable)

Contact details of the specialist to whom the patient was referred for further evaluation of the reported event(s):

Name:.....

Address:.....

Phone number:.....

Annex 6 – Details of Proposed Additional Risk Minimisation Activities (if Applicable)

Patient card:

NOTE:

Here is a proposed patient card agreed by the PRAC. Final card format and content and way of distribution is to be discussed locally with the individual authorities and can therefore be different from the text as described below.

This patient card contains important safety information that you need to be aware of before and during treatment with zoledronic acid *(relevant product name)* injections for cancer-related conditions

Your doctor has recommended that you receive zoledronic acid *(relevant product name)* injections to help prevent bone complications (e.g. fractures) caused by bone metastases, or bone cancers <*and additional indications as appropriate, using the same wording as in the approved package leaflet*>.

A side effect called osteonecrosis of the jaw (ONJ) (bone damage in the jaw) has been reported <*frequency from product information*> in patients receiving zoledronic acid *(relevant product name)* injections for cancer-related conditions. ONJ can also occur after stopping treatment.

In order to reduce the risk of developing osteonecrosis of the jaw, there are some precautions you should take:

Before starting treatment:

- Ask your doctor to tell you about ONJ before you start treatment.
- Check with your doctor whether a dental examination is recommended before you start treatment with zoledronic acid *(relevant product name).*
- Tell your doctor/nurse (health care professional) if you have any problems with your mouth or teeth.

Patients undergoing dental surgery (e.g. tooth extractions), who do not receive routine dental care or have gum disease, are smokers, who get different types of cancer treatments or who were previously treated with a bisphosphonate (used to treat or prevent bone disorders) may have a higher risk of developing ONJ.

While being treated:

- You should maintain good oral hygiene, make sure your dentures fit properly and receive routine dental check-ups.
- If you are under dental treatment or will undergo dental surgery (e.g. tooth extractions), inform your doctor and tell your dentist that you are being treated with zoledronic acid *(relevant product name).*
- Contact your doctor and dentist immediately if you experience any problems with your mouth or teeth such as loose teeth, pain or swelling, non-healing of sores or discharge, as these could be signs of osteonecrosis of the jaw.

Read the package leaflet for further information.