EU-Risk Management Plan (RMP) for ZADENVI (Denosumab biosimilar)

RMP No.: L07/25

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The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV.

QPPV name: Ludmila FILIPOVÁ, MD

QPPV signature: The electronic signature is available on file.

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List of abbreviations

ADR	Adverse drug reaction
ADT	Androgen deprivation therapy
AESI	Adverse events of special interest
AFF	Atypical femoral fracture
AIDS	Acquired immune deficiency syndrome
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
BCVA	Best corrected visual acuity
BMD	Bone mineral density
COPD	Chronic obstructive pulmonary disease
DLP	Data lock point
DXA	Dual-energy X-ray absorptiometry
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
FDA	Food and Drug Administration
GC	Glucocorticoid
GIOP	Glucocorticoid-induced osteoporosis
HALT	Hormone ablation therapy
HIV	Human immunodeficiency virus
HR	Hazard ratio
IBD	Inflammatory bowel disease
IgE	Immunoglobulin E
IgG	Immunoglobulin G
INN	International Non-proprietary Name
LHRH	Luteinizing hormone releasing hormone
LOCS III	Lens Opacities Classification System III
MAH	Marketing authorization holder
MedDRA	Medical Dictionary far Regulatory Activities
MI	Myocardial infarction
MOP	Male osteoporosis

NO	Nuclear opalescence
OI	Osteogenesis imperfecta
ONJ	Osteonecrosis of the jaw
OPG	Osteoprotegerin
OPG-Fc	Osteoprotegerin bound to Fe
P	Posterior subcapsular
PBRER	Periodic benefit-risk evaluation report
PI	Product Information
PIP	Paediatric Investigation Plan
PMO	Postmenopausal osteoporosis
PL	Package leaflet
PMR	Polymyalgia rheumatica
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic safety update report
PTH	Parathyroid hormone
Q3M	Every 3 months
Q6M	Every 6 months
QD	Once a day
QPPV	Qualified Person for Pharmacovigilance
RA	Rheumatoid arthritis
RANKL	RANK ligand
RMP	Risk management plan
SC	Subcutaneous(ly)
SmPC	Summary of product characteristics
SOC	System organ class
US	United States
WHO	World Health Organization

PART I: Product(s) overview

Active substance(s) (INN or common name)	Denosumab biosimilar
Pharmacotherapeutic group(s) (ATC code)	Drugs for treatment of bone diseases – Other drugs affecting bone structure and mineralisation (M05BX04)
Marketing authorisation applicant	Zentiva k.s.
Medicinal product(s) to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	ZADENVI 60 mg solution for injection in pre-filled syringe
Marketing authorisation procedure	Centralised (EMEA/H/C/0006377)
Brief description of the product	Chemical class Denosumab biosimilar, the active substance of ZADENVI, is an immunoglobulin IgG2 isotype monoclonal antibody.
	Summary of mode of action Denosumab biosimilar is a human monoclonal antibody (IgG2) that targets and binds with high affinity and specificity to RANKL, preventing activation of its receptor, RANK, on the surface of osteoclast precursors and osteoclasts. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function, and survival, thereby decreasing bone resorption in cortical and trabecular bone.
	Important information about its composition Denosumab is a human monoclonal IgG2 antibody produced in a mammalian cell line (Chinese hamster ovary cells) by recombinant DNA technology.
Hyperlink to the Product Information	eCTD Module 1.3.1
Indication(s) in the EEA	Current: Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures. In postmenopausal women denosumab biosimilar significantly reduces the risk of vertebral, non-vertebral and hip fractures. Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. In men

	with prostate cancer receiving hormone ablation, denosumab biosimilar significantly reduces the risk of vertebral fractures. Treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture.
	Proposed: Not applicable
Dosage in the EEA	Current: Not applicable
	Proposed: **General recommendations:** The recommended dose of ZADENVI is 60 mg administered as a single subcutaneous injection once every 6 months into the thigh, abdomen or upper arm. The optimal total duration of antiresorptive treatment for osteoporosis (including both denosumab and bisphosphonates) has not been established. The need for continued treatment should be re-evaluated periodically based on the benefits and potential risks of denosumab on an individual patient basis, particularly after 5 or more years of use.
Pharmaceutical form(s) and strength(s)	Current: Not applicable
	Proposed: Solution for injection in pre-filled syringe. Each pre-filled syringe contains 60 mg of denosumab in 1 mL of solution (60 mg/mL).
Will the product be subject to additional monitoring in the EU?	Yes

PART II: Safety Specification

PART II: Module SI-Epidemiology of indications (s) and target population (s)

Based on the Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (Rev. 2), this module is not applicable for the medicinal product(s) seeking a marketing authorisation according to Article 10(4) of Directive 2001/83/EC, as amended.

PART II: Non-clinical part of the safety specification

The non-clinical development programme for ZADENVI was conducted in line with the European Medicines Agency (EMA) Guideline on similar medicinal products containing biotechnology-derived proteins as active substance [1] and the International Council for Harmonisation (ICH) S6(R1) guideline on Preclinical safety evaluation of biotechnology-derived pharmaceuticals [2]. Based on these guidelines, no safety pharmacology, genotoxicity, reproduction toxicology, and carcinogenicity studies are required for non-clinical testing of biosimilars and have not been conducted for ZADENVI .

No factors of concern have been identified with the similarity data obtained for denosumab biosimilar. The data from the exhaustive extended characterization of MB09 comparatively to RP have been analyzed and supports the high similarity of MB09 to its RP notwithstanding minor differences which are not clinically meaningful.

A detailed description of non-clinical development programme for ZADENVI is provided in the eCTD Module 2.

The non-clinical safety profile of Denosumab biosimilar is based on the safety profile of denosumab, supported by the development programme for Denosumab biosimilar as applicable.

PART II: Module SIII - Clinical trial exposure

The clinical development programme for ZADENVI consists of one completed Phase I clinical trial in healthy volunteers (MB09-A-01-19), and one ongoing (main treatment period completed) Phase III clinical trial in postmenopausal women with osteoporosis (Study MB09-C-01-19):

Study MB09-A-01-19 is a Phase I, double-blind, randomised, single-dose, bioequivalence study to compare the PK, PD, safety, and immunogenicity of MB09 (proposed denosumab biosimilar) and EU-/US-sourced Xgeva® in 3 parallel arms of Healthy Male Volunteers.

Study MB09-C-01-19 is a Phase III, randomised, double-blind, parallel, multicentre, multinational study to compare the efficacy, pharmacokinetics, pharmacodynamics, safety and immunogenicity of MB09 versus Prolia® (EU-sourced) in postmenopausal women with osteoporosis. This study is still ongoing (main treatment period completed).

A total of 810 patients and healthy volunteers were enrolled in the Denosumab biosimilar clinical development programme. Of these, 85 subjects received MB09 (the proposed denosumab biosimilar), 85 subjects received EU sourced Xgeva® and 85 received US-sourced Xgeva®. In study MB09-A-01-19, 277 patients received MB09 and 278 subjects received EU-sourced Prolia®.

The clinical design of the MB09-C-01-19 study consisted of two phases: the Main Treatment Period (Day 1 to Month 12), which included two doses of the study treatment administered on Day 1 and at Month 6, and the Transition/Safety Follow-up Period (Month 12 to Month 18/end of study [EOS]), which included a third dose of the study treatment at Month 12. For the results of the Main Treatment Period, subjects were categorized by treatment group (MB09 versus Prolia) up to Month 12. During the Transition/Safety Follow-up Period (referred to as the 'Transition Period'), safety data were summarized by treatment arms as follows: MB09-MB09 (Arm 1), Prolia-MB09 (Arm 2), and Prolia-Prolia (Arm 3). Consequently, the third dose remained the same for patients who initially received MB09 (Arm 1), whereas in one of the Prolia-treated groups (Arm 2), the third dose was switched to MB09. In contrast, the third dose in the other Prolia group (Arm 3) remained unchanged“

Table 1 Cumulative subject exposure to MB09 from clinical trial MB09-A-01-19 by age, sex, race, ethnicity, height, weight, and body mass index.

Demographic and Baseline Characteristics
Safety Population

	MB09 (N=85)	EU Xgeva (N=85)	US Xgeva (N=85)	Overall (N=255)
Age (years)				
n	85	85	85	255
Mean (SD)	40.5 (6.93)	38.8 (6.59)	39.4 (7.15)	39.5 (6.90)
Median	39.0	37.0	39.0	39.0
Min, Max	28,54	28,52	28,55	28,55
Sex, n (%)				
Male	85 (100.0)	85 (100.0)	85 (100.0)	255 (100.0)
Race, n (%)				
White	85 (100.0)	85 (100.0)	85 (100.0)	255 (100.0)
Ethnicity, n (%)Not Hispanic or Latino	85 (100.0)	85 (100.0)	85 (100.0)	255 (100.0)
Height (cm)				
n	85	85	85	255
Mean (SD)	179.07 (6.098)	179.20 (6.662)	177.72 (5.857)	178.66 (6.227)
Median	179.00	179.20	177.00	179.00
Min, Max	163.0, 194.0	157.0, 198.0	164.0, 194.0	157.0, 198.0
Weight (kg)				
n	85	85	85	255
Mean (SD)	83.68 (8.550)	82.74 (8.334)	82.48 (8.643)	82.97 (8.492)
Median	84.70	83.50	83.20	83.50
Min, Max	63.6, 95.0	60.1, 95.0	60.0, 95.0	60.0, 95.0
Body Mass Index (kg/m2)				
n	85	85	85	255
Mean (SD)	26.13 (2.441)	25.76 (2.344)	26.05 (2.415)	25.98 (2.396)
Median	26.40	25.90	26.70	26.30
Min, Max	18.9, 29.9	20.5, 29.8	18.8, 29.8	18.8, 29.9

Note: MB09: MB09 vial containing 70 mg/mL (Study Arm 1, test)
EU Xgeva: EU-sourced Xgeva® vial containing 70 mg/mL (Study Arm 2, reference)
US Xgeva: US-sourced Xgeva® vial containing 70 mg/mL (Study Arm 3, reference) Percentages are based on the number of subjects in the safety population.
Source Data: Listing 16.2.4.1

Table 2. Cumulative subject exposure to MB09 from clinical trial MB09-C-01-19 by age, age group, sex and smoking status – Main treatment period

Demographics and Baseline Characteristics – Main Treatment Period
Safety Analysis Set

	MB09 (N=277)	Prolia (N=278)	Total (N=555)
Age (years)			
n	277	278	555
Mean (SD)	65.8 (6.00)	65.9 (5.90)	65.8 (5.94)
Median	66.0	66.0	66.0
Min, Max	55, 80	55, 80	55, 80
Age Group (years), n (%)			
>= 55 to < 68	170 (61.4)	172 (61.9)	342 (61.6)
>= 68 to <= 80	107 (38.6)	106 (38.1)	213 (38.4)
Sex, n (%)			
Female	277 (100.0)	278 (100.0)	555 (100.0)
Smoking Status, n (%)			
Current Smoker	67 (24.2)	65 (23.4)	132 (23.8)
Former Smoker	39 (14.1)	35 (12.6)	74 (13.3)
Never-Smoker	171 (61.7)	178 (64.0)	349 (62.9)

SD=Standard Deviation; BMD=Bone Mineral Density; BMI=Body Mass Index; CRF=Case Report Form; IRT=Interactive Response Technology.
[1] BMI is calculated as weight (kg) divided by squared height (m).
[2] Prior use of bisphosphonates includes oral bisphosphonate use prior to screening, intravenous bisphosphonate use within 5 years of screening as reported on Bisphosphonates form and prior bisphosphonates (i.e. those with the stop date prior to the first dose of the Main Treatment Period) reported on Prior and Concomitant Medications form.
[3] Fracture history includes fractures reported on Medical and Disease History forms.
[4] Percentages are calculated out of those who have had a fracture.
Source Data: Listing 16.2.4.1

Table 3. Cumulative subject exposure to MB09 from clinical trial MB09-C-01-19 by age, age group, sex and smoking status – Transition period

Demographics and Baseline Characteristics – Transition Period
Safety Analysis Set for Transition Period

	MB09 => MB09 (N=244)	Prolia => MB09 (N=130)	Prolia => Prolia (N=123)	Total (N=497)
Age (years)				
n	244	130	123	497
Mean (SD)	65.5 (5.86)	66.1 (6.04)	65.7 (5.74)	65.7 (5.87)
Median	66.0	66.0	65.0	66.0
Min, Max	55, 80	55, 80	55, 80	55, 80
Age Group (years), n (%)				
>= 55 to < 68	156 (63.9)	80 (61.5)	77 (62.6)	313 (63.0)
>= 68 to <= 80	88 (36.1)	50 (38.5)	46 (37.4)	184 (37.0)
Sex, n (%)				
Female	244 (100.0)	130 (100.0)	123 (100.0)	497 (100.0)
Smoking Status, n (%)				
Current Smoker	60 (24.6)	29 (22.3)	31 (25.2)	120 (24.1)
Former Smoker	34 (13.9)	20 (15.4)	9 (7.3)	63 (12.7)
Never-Smoker	150 (61.5)	81 (62.3)	83 (67.5)	314 (63.2)

SD=Standard Deviation; BMD=Bone Mineral Density; BMI=Body Mass Index.
[1] BMI is calculated as weight (kg) divided by squared height (m).
[2] Prior use of bisphosphonates includes oral bisphosphonate use prior to screening, intravenous bisphosphonate use within 5 years of screening as reported on Bisphosphonates form and prior bisphosphonates (i.e. those with the stop date prior to the first dose of the Main Treatment Period) reported on Prior and Concomitant Medications form.
[3] Fracture history includes fractures reported on Medical and Disease History forms.
[4] Percentages are calculated out of those who have had a fracture.
Source Data: Listing 16.2.4.1

Table 4. Cumulative subject exposure to MB09 from clinical trial MB09-C-01-19 by race and ethnicity- Main Treatment period

Demographics and Baseline Characteristics – Main Treatment Period
Safety Analysis Set

	MB09 (N=277)	Prolia (N=278)	Total (N=555)
Race, n (%)			
White	276 (99.6)	275 (98.9)	551 (99.3)
Black or African American	0	0	0
Asian	0	0	0
American Indian or Alaska Native	1 (0.4)	3 (1.1)	4 (0.7)
Native Hawaiian or Other Pacific Islander	0	0	0
Not to be collected as per regulations	0	0	0
Other	0	0	0
Multiple	0	0	0
Ethnicity, n (%)			
Hispanic or Latino	10 (3.6)	13 (4.7)	23 (4.1)
Not Hispanic or Latino	267 (96.4)	265 (95.3)	532 (95.9)

SD=Standard Deviation; BMD=Bone Mineral Density; BMI=Body Mass Index; CRF=Case Report Form; IRT=Interactive Response Technology.
[1] BMI is calculated as weight (kg) divided by squared height (m).
[2] Prior use of bisphosphonates includes oral bisphosphonate use prior to screening, intravenous bisphosphonate use within 5 years of screening as reported on Bisphosphonates form and prior bisphosphonates (i.e. those with the stop date prior to the first dose of the Main Treatment Period) reported on Prior and Concomitant Medications form.
[3] Fracture history includes fractures reported on Medical and Disease History forms.
[4] Percentages are calculated out of those who have had a fracture.
Source Data: Listing 16.2.4.1

Table 5. Cumulative subject exposure to MB09 from clinical trial MB09-C-01-19 by race and ethnicity- Transition period

Demographics and Baseline Characteristics – Transition Period
Safety Analysis Set for Transition Period

	MB09 -> MB09 (N=244)		Prolia -> MB09 (N=130)		Prolia -> Prolia (N=123)		Total (N=497)	
Race, n (%)								
White	243	(99.6)	127	(97.7)	123	(100.0)	493	(99.2)
Black or African American	0		0		0		0	
Asian	0		0		0		0	
American Indian or Alaska Native	1	(0.4)	3	(2.3)	0		4	(0.8)
Native Hawaiian or Other Pacific Islander	0		0		0		0	
Not to be collected as per regulations	0		0		0		0	
Other	0		0		0		0	
Multiple	0		0		0		0	
Ethnicity, n (%)								
Hispanic or Latino	8	(3.3)	7	(5.4)	5	(4.1)	20	(4.0)
Not Hispanic or Latino	236	(96.7)	123	(94.6)	118	(95.9)	477	(96.0)

SD=Standard Deviation; BMD=Bone Mineral Density; BMI=Body Mass Index.
[1] BMI is calculated as weight (kg) divided by squared height (m).
[2] Prior use of bisphosphonates includes oral bisphosphonate use prior to screening, intravenous bisphosphonate use within 5 years of screening as reported on Bisphosphonates form and prior bisphosphonates (i.e. those with the stop date prior to the first dose of the Main Treatment Period) reported on Prior and Concomitant Medications form.
[3] Fracture history includes fractures reported on Medical and Disease History forms.
[4] Percentages are calculated out of those who have had a fracture.
Source Data: Listing 16.2.4.1

Table 6. Cumulative subject exposure to MB09 from clinical trial MB09-C-01-19 by baseline height, weight and BMI- Main treatment period

Demographics and Baseline Characteristics – Main Treatment Period
Safety Analysis Set

	MB09 (N=277)	Prolia (N=278)	Total (N=555)
Baseline Height (cm)			
n	277	278	555
Mean (SD)	159.97 (6.252)	159.99 (6.131)	159.98 (6.186)
Median	160.00	160.00	160.00
Min, Max	144.0, 174.1	138.0, 180.0	138.0, 180.0
Baseline Weight (kg)			
n	277	278	555
Mean (SD)	63.063 (8.8299)	63.328 (8.7580)	63.196 (8.7870)
Median	62.100	62.500	62.400
Min, Max	48.60, 90.30	48.40, 96.80	48.40, 96.80
Baseline BMI (CRF) (kg/m^2) [1]			
n	277	278	555
Mean (SD)	24.629 (3.0184)	24.737 (3.0661)	24.683 (3.0401)
Median	24.200	24.300	24.200
Min, Max	18.10, 35.40	18.10, 35.90	18.10, 35.90

SD=Standard Deviation; BMD=Bone Mineral Density; BMI=Body Mass Index; CRF=Case Report Form; IRT=Interactive Response Technology.
[1] BMI is calculated as weight (kg) divided by squared height (m).
[2] Prior use of bisphosphonates includes oral bisphosphonate use prior to screening, intravenous bisphosphonate use within 5 years of screening as reported on Bisphosphonates form and prior bisphosphonates (i.e. those with the stop date prior to the first dose of the Main Treatment Period) reported on Prior and Concomitant Medications form.
[3] Fracture history includes fractures reported on Medical and Disease History forms.
[4] Percentages are calculated out of those who have had a fracture.
Source Data: Listing 16.2.4.1

Table 7. Cumulative subject exposure to MB09 from clinical trial MB09-C-01-19 by baseline

Demographics and Baseline Characteristics – Transition Period
Safety Analysis Set for Transition Period

	MB09 => MB09 (N=244)	Prolia => MB09 (N=130)	Prolia => Prolia (N=123)	Total (N=497)
Baseline Height (cm)				
n	244	130	123	497
Mean (SD)	159.92 (6.240)	159.25 (5.686)	160.73 (6.426)	159.94 (6.158)
Median	160.00	159.95	161.00	160.00
Min, Max	144.0, 174.0	138.0, 174.0	144.0, 180.0	138.0, 180.0
Baseline Weight (kg)				
n	244	130	123	497
Mean (SD)	63.00 (8.509)	63.14 (8.381)	63.03 (8.980)	63.04 (8.578)
Median	62.05	62.85	62.00	62.00
Min, Max	50.0, 90.3	50.1, 87.0	48.4, 96.8	48.4, 96.8
Baseline BMI (CRF) (kg/m^2) [1]				
n	244	130	123	497
Mean (SD)	24.63 (2.929)	24.89 (2.957)	24.39 (3.069)	24.64 (2.971)
Median	24.20	24.60	24.10	24.20
Min, Max	18.1, 30.6	18.7, 30.1	18.1, 30.5	18.1, 30.6

SD=Standard Deviation; BMD=Bone Mineral Density; BMI=Body Mass Index.
[1] BMI is calculated as weight (kg) divided by squared height (m).
[2] Prior use of bisphosphonates includes oral bisphosphonate use prior to screening, intravenous bisphosphonate use within 5 years of screening as reported on Bisphosphonates form and prior bisphosphonates (i.e. those with the stop date prior to the first dose of the Main Treatment Period) reported on Prior and Concomitant Medications form.
[3] Fracture history includes fractures reported on Medical and Disease History forms.
[4] Percentages are calculated out of those who have had a fracture.
Source Data: Listing 16.2.4.1

PART II: Module SIV- Populations not studied in clinical trials

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

Exclusion criteria within the clinical development programme for Denosumab biosimilar were based on the exclusion criteria within the original development programme for Denosumab biosimilar to Prolia® and Xgeva® on the known safety profile of denosumab reference medicinal product.

The main exclusion criteria from the Study MB09-C-01-19 were based on the known safety profile of Prolia®. The main criteria are summarised below.

Table 8. Exclusion criteria in the clinical trial MB09-C-01-19

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Hypocalcemia	Hypocalcemia must be corrected by adequate intake of calcium and vitamin D before initiating therapy. Patients receiving denosumab must have adequate intake of calcium and vitamin D. this information is provided in the Summary of Product Characteristics (SmPC).	No	It is a contraindication in the Summary of Product Characteristics (SmPC) for Prolia® .
Hypersensitive to the active substance or to any of the excipients	Patients who are hypersensitive to denosumab or to any of the excipients should not receive this medication.	No	It is a contraindication in the SmPC.
Other bones diseases	Patients with other bone diseases such as RA, and Paget's disease were excluded from the pivotal osteoporosis studies because other bone diseases could confound the efficacy results.	No	Prolia® is not indicated for use in these other patient populations. However, subjects with RA were not excluded from the pivotal study in the GIOP population (Study 20101217), because RA is a common indication for GC use

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Previous bisphosphonate treatment	Subjects with previous bisphosphonate treatment were excluded from pivotal osteoporosis studies in accordance with regulatory guidance to demonstrate fracture benefit in a PMO population. Because bisphosphonates incorporate into bone and long-term use of bisphosphonates is associated with continued effects of the drug after treatment is stopped, it was deemed most appropriate to exclude previous bisphosphonate treatment.	No	In Study 20050234, a double-blind, alendronate-controlled, in postmenopausal women with low BMD who had received bisphosphonates for at least 6 months preceding study entry, safety results were similar in the denosumab and alendronate treatment groups. In addition, Studies 20080099, 20080562, and 20110153 evaluated the effects of denosumab and a bisphosphonate (risedronate, ibandronate, or zoledronic acid, respectively) in postmenopausal women transitioning from previous bisphosphonate therapy. There were no new safety findings in these studies.
Evidence of distant metastases	Subjects with distant metastases have been evaluated in other clinical studies of denosumab using a different dose and schedule (up to 120 mg monthly).	No	An indication in this patient population was not sought for denosumab 60 mg. Denosumab 120 mg is approved for prevention of skeletal-related events in adults with bone metastases from solid tumours; thus, safety in this population is well documented.
Serum creatinine > 2.0 mg/dL	Treatment with antiresorptive agents reduces the ability to mobilize calcium from bone; thus,	No	Study 20040245 demonstrated that renal impairment does not affect the pharmacokinetics of denosumab; therefore, no dose

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
	hypocalcaemia could be exacerbated in patients with renal impairment.		adjustments are required in patients with impaired renal function. Recommendations for adequate intake of calcium and vitamin D in all patients, and recommendations for monitoring of serum calcium in patients predisposed to hypocalcemia, have been included in the SmPC. No other special dosing recommendations are considered necessary for subjects with renal impairment.
Subjects who are pregnant or breastfeeding or planning to become pregnant	Adequate and well-controlled studies with denosumab have not been conducted in pregnant women due to the potential risk to the fetus. It is not known whether denosumab is transferred into human milk.	No	These populations are not included in the intended indications. Risk minimization via product labelling instructing patients to avoid pregnancy and breast feeding is in place. No additional pharmacovigilance activities or additional risk minimization are warranted.
Oral or dental conditions: osteomyelitis or history and/or presence of osteonecrosis of the jaw	It is considered as a risk factor for the development of ONJ.	No	It is a contraindication in the SmPC.

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

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, those caused by prolonged or cumulative exposure, or adverse reactions with a long latency. The table below shows limitations of adverse drug reactions detection common to clinical development programmes.

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

Table 9. Exposure of special populations included or not in clinical trial development programmes.

Type of special population	Exposure
Elderly patients	Refer to PART II: Module SIII (Table 1, 2 and 3)
Pregnant or breastfeeding women	Not included in the clinical development programme
Patients with relevant comorbidities: – Patients with hepatic impairment – Patients with renal impairment	Not included in the clinical development programme
Population with relevant different ethnic origin	There is no preclinical or clinical data to date suggesting differences in the RANKL/RANK interaction and mode of action related to the inhibition of the osteoclast formation, function and survival and their corresponding effect in bone resorption (cortical and trabecular bone) in patients of different ethnic origin.
Subpopulations carrying known and relevant polymorphisms	Not included in the clinical development programme

PART II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

Not applicable since this is the first Risk Management Plan.

SV.1.1 Method used to calculate exposure

Not applicable since this is the first Risk Management Plan.

PART II: Module SVI - Additional EU requirements for Safety Specification

Potential for misuse for illegal purposes

ZADENVI does not have any potential for misuse for illegal purposes.

PART II: Module SVII- Identified and Potential Risks

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

ZADENVI is a biosimilar product to the reference medicinal product Prolia® [3]. Therefore, the safety profile of ZADENVI is based on the general safety profile of denosumab, which resulted from the extensive experience with Prolia® (authorised in the EU on 26 May 2010).

Overall, the development programme for ZADENVI did not raise new safety concerns and all clinically relevant adverse effects reported in the respective clinical studies corresponded to the known safety profile of denosumab (for full information on reported adverse events within the clinical development programme for ZADENVI, refer to eCTD Module 2.7.4 Summary of Clinical Safety). The immunogenicity of ZADENVI was considered as part of its clinical development programme and results will be analysed once ongoing study would be finalized.

Immunogenicity is not a safety concern of Prolia®, and it does not represent a newly raised safety concern for ZADENVI.

This RMP for ZADENVI is consequently based on the RMP for PROLIA® (version 31.0, Jan 2023)

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

According to RMP for PROLIA® (version 31.0, Jan 2023) no risks are considered for inclusion in this section.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

All safety concerns in the RMP for the biosimilar product ZADENVI are solely based on the safety concerns for Prolia®

Important identified risks:

- Hypocalcemia
- Skin infection leading to hospitalisation
- Osteonecrosis of the jaw
- Hypersensitivity reactions
- Atypical femoral fracture
- Hypercalcemia in pediatric patients receiving Denosumab and after treatment discontinuation.

Important potential risks

- Fracture healing complications
- Infection
- Cardiovascular events
- Malignancy

Missing information:

- None

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

SVII.3.1.1 INFORMATION ON IMPORTANT IDENTIFIED RISKS

SVII. 3.1.1.1 Hypocalcemia

Potential mechanism(s):

Denosumab inhibits osteoclast bone resorption, thereby decreasing the release of calcium from bone into the bloodstream.

Evidence source(s) and strength of evidence:

This risk was identified in the phase III, randomized, double-blind, placebo- or active-controlled studies.

Characterisation of the risk:

Frequency

In the pooled pivotal studies for PMO and HALT from Prolia® subject incidence of hypocalcemia adverse events was < 0.1% in denosumab-treated subjects and 0.1% in placebo-treated subjects. The incidence of hypocalcemia adverse events was lower in denosumab -treated subjects than in placebo-treated subjects; thus, 95% CIs were not calculated. In the 24-month final analysis of the GIOP study from Prolia®, subject incidence of hypocalcemia adverse events was 0.3% in the denosumab group; there were no adverse events of hypocalcemia in the risedronate group thus, 95 % CIs were no calculated.

Severity

While most hypocalcemia events are mild to moderate in severity; severe events have occurred.

Reversibility

Hypocalcemia is reversible when treated with oral calcium and vitamin D supplementation. In severe cases, IV calcium supplementation may be required.

Long-term outcomes

No long-term complications are anticipated for properly treated hypocalcemia.

Impact on quality of life

For severe symptomatic hypocalcemia, patients may be hospitalized for treatment. Generally, patients recover when their hypocalcemia is treated.

Risk factors and risk groups:

Risk factors include severe renal impairment and hyperphosphatemia. Other risks factors may include a history of hypoparathyroidism, PTH resistance, vitamin D deficiency or resistance, thyroid surgery, parathyroid surgery, malabsorption syndromes, excision of small intestine, severe renal impairment (CrCL<30 mL/min), dialysis, and some medications [12]

Preventability:

Pre-existing hypocalcaemia should be corrected by adequate intake of calcium and vitamin D before initiating therapy, and supplementation with calcium and vitamin D is important during therapy in all patients receiving denosumab. Clinical monitoring of calcium levels is recommended during treatment, especially in those with renal impairment.

Impact on the risk-benefit balance of the product:

The risk of hypocalcemia has been considered in the product benefit-risk assessment. Considering the product labelling addressing the risk, the overall benefit-risk balance is considered to be positive.

Public health impact:

Significant public health impact is not expected as this risk is preventable and treatable with the appropriate risk mitigating measures communicated clearly in the SmPC.

SVII. 3.1.1.2 Skin infection leading to hospitalisation

Potential mechanism(s):

Keratinocytes can express RANKL and blocking RANKL in mice decreased the number of regulatory T-cells in skin, leading to an increased inflammatory response [29]

Evidence source(s) and strength of evidence:

The risk was identified in the phase III, randomized, double-blind, placebo-or active-controlled studies.

Characterisation of the risk:

Frequency

In pooled PMO/HALT pivotal studies from Prolia®, subject incidence of skin infection was 1.4% with denosumab and 1.3% with placebo; the hazard ratio (HR) was 1.09 (95% CI:0.78,1.53). Subject incidence of serious adverse events of skin infection was 0.4% with denosumab and 0.2 % with placebo (HR [95% CI] =2.55 [1.13, 5.76]. In the 24-month final analysis of the GIOP study from Prolia®, subject incidence of adverse events of skin infection was 1.8% with denosumab and 0.5% with risedronate; the HR was 3.62 (95% CI=0.75, 17.42). Subject incidence of serious adverse events of skin infection was 0.5% in both the denosumab and risedronate groups (HR [95% CI] = 1.03[0.15, 7.34])

Severity

Serious adverse events of skin infection were mostly severe in intensity.

Reversibility

These events typically resolved with administration of antibiotics.

Long-term outcomes

No long-term complications are anticipated for properly treated patients who are hospitalized due to skin infections.

Impact on quality of life

Requires a hospital stay; patients generally recover with antibiotic treatment.

Risk factors and risk groups:

Risk factors for infection in general include increasing age, immunosuppression associated with cancer, diabetes, HIV/acquired immune deficiency syndrome (AIDS), immunosuppressant drugs (e.g., corticosteroids, arthritis medications, and chemotherapy drugs), substance abuse, and malnutrition. Risk factors for skin infection in older patients include skin wounds, peripheral vascular disease, eczema/dermatitis, and venous stasis disorders.

Preventability:

No preventive measures are known.

Impact on the risk-benefit balance of the product:

The risk of skin infection leading to hospitalisation has been considered in the product benefit-risk assessment. Considering the product labelling addressing the risk, the overall benefit-risk balance is considered to be positive.

Public health impact:

Since frequency of skin infection leading to hospitalisation is relatively low, absolute difference between denosumab and placebo groups is relatively small, and the adverse events can be effectively treated by antibiotics, the negative impact to public health is relatively small.

SVII. 3.1.1.3 Osteonecrosis of the jaw

Potential mechanism(s):

Osteonecrosis of the jaw (ONJ) appears to be multifactorial and multiple hypotheses have been postulated and have included factors such as inhibition of bone remodelling, infection and inflammation, inhibition of angiogenesis, soft tissue toxicity, altered immunity and genetic predisposition. As yet, evidence supporting these hypotheses has been variable and little is understood in how these multiple pathways might interact [5,11]

Evidence source(s) and strength of evidence:

This risk was identified in open-label long-term extensions to phase III, randomized, double-blind, placebo-controlled studies.

Characterisation of the risk:

Frequency

No cases of ONJ have been reported in placebo-controlled studies from Prolia® (although cases were reported in open-label extensions to the pivotal PMO study and a HALT study); thus, 95% CIs were not calculated. No cases of ONJ were reported in the GIOP study from Prolia®.

Overall, across the Amgen-sponsored clinical development program for Prolia®, positively adjudicated ONJ cases have been reported rarely (17 ONJ cases in 23280 subjects, 0.073%) in subjects cumulatively exposed to denosumab (60 mg) clinical studies.

Severity

Most events leading to adjudication as ONJ were assessed as moderate in severity. Mild and severe events were also reported.

Reversibility

In general, ONJ events are clinically reversible with supportive care, antibiotics; however, surgical treatment may be required.

Long-term outcomes

No data on long-term outcomes are available.

Impact on quality of life

Discomfort associated with ONJ lesions and/or with more extensive treatments may impact patient wellbeing via decreased oral intake (e.g., decreased hydration and decreased nutritional intake).

Risk factors and risk groups:

Risk factors include duration of exposure to denosumab, prior bisphosphonate use (particularly for extended periods of time), older age, periodontal disease, dentoalveolar surgery, trauma from poorly fitting dentures, malignancy, chemotherapy, corticosteroids, smoking, systemic or regional infection, immune-compromised state predisposing to increased risk of infection, hypercoagulable state secondary to underlying malignancy, and vascular insufficiency due to thrombosis [18; 22]

Preventability:

A dental examination with appropriate preventive dentistry is recommended prior to treatment with denosumab especially in patients with risk factors. While on treatment, patients should avoid invasive dental procedures where possible. Patients who are suspected of having or who develop ONJ while on denosumab should receive care by a dentist or an oral surgeon. In patients who develop ONJ during treatment with denosumab, a temporary interruption of treatment should be considered based on individual risk/benefit assessment until the condition resolves.

Impact on the risk-benefit balance of the product:

The risk of osteonecrosis of the jaw has been considered in the product benefit-risk assessment. Considering the product labelling and additional risk minimization activities addressing this risk, the overall benefit-risk balance is considered to be positive.

Public health impact:

Significant public health impact is not expected with denosumab, as the event is rare, and the actions taken to minimize the likelihood of developing ONJ are described in the prescribing information.

SVII. 3.1.1.4 Hypersensitivity Reactions

Potential mechanism(s):

Two types of allergic reactions, immunoglobulin E (IgE)- and non-IgE mediated, appear to be related to monoclonal antibody administration. The IgE-mediated reactions can cause both

wheal and flare reactions at the injection site but may also be associated with urticaria and anaphylaxis. The mechanism of non-IgE reactions is unclear.

Evidence source(s) and strength of evidence:

This risk was identified in the postmarketing setting based on a clinically plausible association between administration of denosumab and hypersensitivity reactions.

Characterisation of the risk:

Frequency

In the pooled PMO/HALT pivotal studies from Prolia®, subject incidence of hypersensitivity and drug hypersensitivity was 1.0% in denosumab-treated subjects and 0.8% in placebo-treated subjects; HR= 1.26 (95% CI:0.83, 1.90). Subject incidence of potential clinical consequences of hypersensitivity was 1.3% in both treatment groups; HR=0.94 (95% CI:0.66, 1.33). In the 24-month final analysis of the GIOP study, subject incidence of adverse events potentially associated with hypersensitivity was 6.3% in denosumab-treated subjects and 4.7% in risedronate-treated subjects (HR [95% CI] = 1.41 [0.77, 2.59]

Severity

Most hypersensitivity reactions are mild to moderate in severity; severe events have occurred.

Reversibility

Hypersensitivity reactions are generally reversible with discontinuation of the medication, though treatment may be required.

Long-term outcomes

No long-term complications are anticipated for properly treated hypersensitivity reactions.

Impact on quality of life

For severe hypersensitivity reactions, patients may be treated in the emergency room and/or hospitalized for treatment. Generally, patients recover when denosumab is discontinued with or without additional treatment.

Risk factors and risk groups:

Known hypersensitivity to denosumab and any of its excipients.

Preventability:

No data are available on potential measures to prevent hypersensitivity reactions to denosumab. The appropriate contraindication information on hypersensitivity to denosumab and any of its excipients is included in the SmPC.

Impact on the risk-benefit balance of the product:

The risk of hypersensitivity reactions has been considered in the product benefit-risk assessment. Considering the product labelling addressing this risk, the overall benefit-risk balance is considered to be positive.

Public health impact:

No significant public health impact is expected as reports of severe events (e.g., anaphylaxis) are rare.

SVII. 3.1.1.5 Atypical Femoral Fracture

Potential mechanism(s):

Prolonged suppression of bone turnover may be associated with increased risk of atypical femoral fracture (AFF), but the pathogenesis remains unclear and the causes of AFF are likely multi-factorial. Based on nonclinical studies, collagen cross-linking and maturation, accumulation of microdamage and advanced glycation end products, mineralization, remodelling, vascularity, and angiogenesis lend biologic plausibility to a potential association between these effects and AFF [17 ; 24]

Evidence source(s) and strength of evidence:

This risk was identified in an open-label long-term extension to a phase III, randomized, double-blind, active-controlled study.

Characterisation of the risk:

Frequency

No cases of confirmed AFF have been reported in placebo-controlled studies from Prolia®; thus, 95 % CIs were not calculated. In the GIOP study from Prolia®, subject incidence of confirmed AFF was 0.3% (1 event) in the denosumab group; there were no adverse events of AFF in the risedronate group thus, 95% CIs were not calculated.

Overall, as of 26 September 2016, adjudicated-positive cases of AFF have been reported rarely (5 of 23 280 subjects, 0.021%) in subjects exposed to denosumab (60mg) in clinical studies from Prolia®

Severity

Atypical femoral fracture is a medically important adverse event that generally requires significant medical interventions such as surgery and ongoing monitoring to mitigate risk for and severity of contralateral fractures. The few events from Prolia® studies leading to adjudication of AFF were considered as severe in intensity.

Reversibility

Atypical femoral fracture in generally treatable with surgical intervention. It is unknown if the pathophysiological mechanism(s) contributing to the development of AFF are reversible after treatment is discontinued.

Long-term outcomes

No data on long-term outcomes are available.

Impact on quality of life

As with other femur fractures, AFF can cause short-term or long-term disability. Some data suggests that healing of AFF may be more prolonged than a typical femoral fracture [9, 26]

Risk factors and risk groups

Long-term antiresorptive treatment has been associated with AFF. Corticosteroids have also been reported in the literature to potentially be associated with AFF [14; 20]. Atypical femoral fractures have also been reported in patients with certain comorbid conditions (e.g., vitamin D deficiency, RA, hypophosphatasia) and with use of bisphosphonates, glucocorticoids, and proton pump inhibitors [24]

Preventability:

No data are currently available on potential measures to prevent AFF. Patients using long-term antiresorptives may experience pain over the femur, which requires radiological examination if atypical fracture is suspected.

Impact on the risk-benefit balance of the product:

The risk of atypical femoral fracture has been considered in the product benefit-risk assessment. Considering the product labelling addressing this risk, the overall benefit-risk balance is considered to be positive.

Public health impact:

Based on the infrequency of AFF in patients treated with denosumab, no significant additional public health impact is expected.

SVII. 3.1.1.6 Hypercalcemia in Pediatrics Patients Receiving Denosumab and after treatment discontinuation.

Potential mechanism(s):

The exact mechanism of hypercalcemia occurring in paediatric patients both during the dosing interval and following discontinuation is not certain but may be a consequence of the following, alone, or in combination:

• Hypercalcemia may result from rapid resorption of retained primary spongiosa in a skeleton with active endochondral ossification. The rate of endochondral ossification and duration of exposure to denosumab would determine the amount of accumulated primary spongiosa that could influence the magnitude of resorptive response (mechanostat-driven) and release of calcium from resorbing bone matrix via an autocrine/paracrine mechanism.

• The magnitude of the resorptive response following treatment and withdrawal in the immature skeleton could be dictated by the normal high rate of bone turnover in individuals with growing skeletons.

• The response of the osteoclast lineage to loss of inhibition of osteoclastogenesis may be intrinsically more robust in individuals with growing skeletons. The increased skeletal metabolism related to bone modelling and growth in children is therefore likely to impact to bone modelling and growth in children is therefore likely to impact the frequency of hypercalcemia occurring both between the dosing interval and following discontinuation.

Evidence source(s) and strength of evidence:

Data to evaluate safety concern were derived from Prolia® clinical trials in pediatric subjects with OI, Xgeva® clinical studies, and postmarketing adverse event reporting involving pediatric patients receiving denosumab at unapproved doses and/or unapproved indications for use.

Characterisation of the risk:

Frequency

In the completed pediatric OI studies 20130173 from Prolia® during the Q6M dosing regimen, ≥hypercalcemia (Amgen Medical Dictionary for Regulatory Activities [MedDRA] Query [Narrow Search;AMQB]) was reported for 29 subjects (19.0%). All these events were nonserious.

During the Q3M dosing regimen and following denosumab discontinuation, hypercalcemia (AMQN) was reported for 22 subjects (36.7%). Serious events of hypercalcemia were reported for 8 subjects (13.3%).

Severity

Most subjects in the pediatric OI Study 20130173 from Prolia® receiving the Q3M dosing regimen who had hypercalcemia events experienced mil events. Grade ≥ 3 hypercalcemia was reported for 10 subjects (16.7%). Grade 4 (life-threatening) hypercalcemia was reported for 4 subjects (6.7%)

Reversibility

Hypercalcemia is reversible when treated. In severe cases, use of rescue medications may be required.

Long-term outcomes

No long-term adverse effects are anticipated for properly treated hypercalcemia.

Impact on quality of life

Pediatric patients may present with severe hypercalcemia requiring hospitalization. Generally, patients recover when the hypercalcemia is treated.

Risk factors and risk groups:

Pediatric patients with growing skeletons and high bone turnover disease states (such as OI)

Preventability:

ZADENVI is not indicated in pediatric patients (age < 18years) and should not be used in pediatric patients. If used in a clinical trial setting, such as for pediatric GIOP from Prolia®, monitoring for signs and symptoms and periodic serum calcium is advisable.

Impact on the risk-benefit balance of the product:

The benefit-risk profile of ZADENVI (denosumab) is not favourable in the pediatric patient population.

Public health impact:

Significant public health impact is not expected as this risk is preventable with the appropriate risk mitigating measures communicated clearly in the SmPC.

SVII.3.1.2 Information on important potential risks

SVII.3.1.2.1 Fracture Healing Complications

Potential mechanism(s):

Because denosumab directly suppresses bone resorption and (indirectly) bone formation, it has the theoretical potential to delay fracture healing.

Evidence source(s) and strength of evidence:

This is a theoretical risk based on the mechanism of action.

Characterisation of the risk:

Frequency

Of the subjects who had nonvertebral fractures in the large pivotal PMO study from Prolia®, fracture healing complications (delayed healing or non-union) were reported in 2 of 386

subjects in the denosumab group (0.5%) and 5 of 465 subjects (1.1%) in the placebo group. Of the subjects who had nonvertebral fractures in the pivotal study far HALT-breast cancer from Prolia®, fracture healing complications were reported in 0 of 8 subjects in the denosumab group and 1 of 8 subjects (12.5%) in the placebo group.

Because of the low incidence of fracture healing complications, 95% CIs were not calculated.

No fracture healing complications were reported in the MOP study from Prolia®.

No fracture healing complications were reported in the GIOP study from Prolia®.

Severity

This risk has not been substantiated; however, impaired fracture healing could have significant impact on patient wellbeing.

Reversibility and long-term outcomes

This risk has not been substantiated; however, the effects of denosumab on osteoclasts are fully reversible.

Long-term outcomes

This risk has not been substantiated; however, no long-term impact would be anticipated based on reversibility.

Impact on quality of life

Fracture healing complications can cause short-term or long-term disability. Surgery may be required.

Risk factors and risk groups:

General risk factors for fracture healing complications are thought to include older age, diabetes, use of medications such as non-steroidal anti-inflammatory drugs and corticosteroids, smoking, excessive alcohol use, and poor nutrition [13;16]

Preventability:

No preventive measures are known.

Impact on the risk-benefit balance of the product:

The potential risk of fracture healing complications has been considered in overall assessment supporting a positive benefit-risk profile.

Public health impact:

No significant impact on public health is anticipated.

SVII.3.1.2.2 Infection

Potential mechanism(s):

RANK ligand is expressed on activated T and B cells and in the lymph nodes and some reports have described immune modulatory effects of RANKL inhibition. However, no clinically relevant effect of denosumab treatment was observed on peripheral blood immune cell subset profiles in studies in healthy elderly men, postmenopausal women, and postmenopausal women with low BMD. No evidence of a treatment effect of denosumab on immunoglobulin production was observed.

Evidence source(s) and strength of evidence:

This is considered a potential risk based on theoretical concerns which has not been substantiated in the extensive clinical study program or in the postmarketing experience.

Characterisation of the risk:

Frequency

	Subject Incidence[a] (percent)	Hazard ratio (95% CI)
Adverse events		
Placebo	50.6	0.98 (0.92, 1.03)
Denosumab	50.1	
Serious adverse events		
Placebo	3.4	1.25 (1.02, 1.53)
Denosumab	4.3	
Serious adverse events not including skin infection		
Placebo	3.3	1.18 (0.95, 1.45)
Denosumab	3.9	
Opportunistic infection		
Placebo	0.1%	--
Denosumab	0.1%	

Table 10. aPooled pivotal studies for PMO (20030216, 20040132) and HALT and 20040138 in prostate cancer and 20040135 in breast cancer, Safety Analysis Set. (source Prolia® RMP)

In the 24-month final analysis of the GIOP study from Prolia®, subject incidence of infections was 36.3% with denosumab and 36.4% with risedronate; HR = 1.06 (0.84, 1.34). Subject incidence of serious adverse events of infection was 5.8% in the denosumab group and 6.5% in the risedronate group (HR [95% CI] = 0.95 [0.54, 1.68]).

Severity

The majority of reported events of infection were non serious. Serious adverse events were most commonly reported as severe in intensity.

Reversibility

Infections when treated appropriately are generally reversible.

Long-term outcomes

Infection generally responds to appropriate treatment and as such no long-term effects are anticipated.

Impact on quality of life

For severe infection, patients may be hospitalized for treatment.

Generally, patients recover when their infection is treated.

Risk factors and risk groups:

Risk factors for infection in general include increasing age immunosuppression associated with cancer, diabetes, HIV/AIDS, immunosuppressant drugs (e.g., corticosteroids, arthritis medications, and chemotherapy drugs), substance abuse, and malnutrition.

Preventability:

No preventive measures are known.

Impact on the risk-benefit balance of the product:

The potential risk of infection has been considered in the overall assessment which supports a positive benefit-risk profile in the indicated populations.

Public health impact:

No significant public health impact is expected for this unsubstantiated risk as effective treatments are available.

SVII.3.1.2.3 Cardiovascular events

Potential mechanism(s):

Elevated levels of OPG have been associated with coronary artery disease in cross-sectional studies but this association has been contradicted by preclinical and epidemiological studies demonstrating that the lack of OPG or unopposed RANKL is associated with cardiac calcification. Because of these conflicting results and because denosumab inhibits RANKL, a theoretical concern for denosumab to affect progression of atherosclerosis exists.

Evidence source(s) and strength of evidence:

This is a theoretical risk based on epidemiological data demonstrating elevated OPG in patients with cardiovascular disease.

Characterisation of the risk:

Frequency

In a pooled analysis of the large pivotal PMO study (20030216) and the pivotal HALT-prostate study from Prolia®, the overall subject incidence of adjudicated-positive serious cardiovascular events was 5.8% with denosumab and 5.6% with placebo (HR [95% CI] = 1.00 [0.85, 1.19]).

The subject incidence of positively adjudicated, pre-defined categories of serious cardiovascular event was comparable between the treatment groups in the pooled analysis, as shown below:

Studies 20030216 and 20040138	Subject Incidence (percent)	Hazard ratio (95% CI)
Acute coronary syndrome		
Placebo	1.4	0.96 (0.68, 1.35)
Denosumab	1.4	
Congestive heart failure		
Placebo	0.7	1.03 (0.64, 1.65)
Denosumab	0.8	
Stroke/transient ischemic attack		
Placebo	1.5	1.06 (0.77, 1.46)
Denosumab	1.7	
Arrhythmia		
Placebo	1.3	1.15 (0.82, 1.63)
Denosumab	1.5	
Other vascular disorders		
Placebo	0.9	1.13 (0.75, 1.71)
Denosumab	1.1	
Cardiovascular death		
Placebo	1.1	0.79 (0.52, 1.18)
Denosumab	0.9	

Table 11. Subject incidence in Studies 20030216 and 20040138 (source Prolia® RMP)

During the placebo-controlled phase of the pivotal study for MOP from Prolia®, adverse events in the cardiac disorders system organ class (SOC) were reported in 8 (6.7%) denosumab-treated and 3 (2.5%) placebo-treated subjects (note: 2 events of angina tonsillitis in the denosumab group were incorrectly coded to the cardiac disorders adverse event category). The incidence of adverse events in the vascular disorders SOC was 5.0% in denosumab-treated and 6.7% in placebo-treated subjects.

In the GIOP study from Prolia®, adverse events in the cardiovascular disorders or vascular disorders SOC were reported in 65 (16.5%) denosumab-treated subjects and 53 (13.8%) risedronate-treated subjects. (HR [95% CI] = 1.27 [0.88, 1.82]). Subject incidence of serious adverse events in the cardiovascular or vascular SOC was 3.8% on the denosumab group and 3.9% in the risedronate group.

In Study 20190038 (a retrospective cohort study assessing the incidence of cardiovascular and cerebrovascular events among postmenopausal women and men with osteoporosis treated with denosumab or zoledronic acid for up to 36 months of treatment) from Prolia®, the unadjusted incidence rates of myocardial infarction, stroke, and MI-stroke composite outcome were 0.23 to 0.72 per 100 person-years. The differences in the unadjusted incidence rates of outcome between denosumab and zoledronic acid treatment groups were small (< 0.1 risk difference).

Severity

This risk has not been substantiated; however, cardiovascular events may be severe/life-threatening.

Reversibility

This risk has not been substantiated; however, effects of denosumab to block RANKL are fully reversible.

Long-term outcomes

This risk has not been substantiated; however, cardiovascular events could impact patient long-term outcome.

Impact on quality of life

Cardiovascular disease varies greatly in severity. For severe disease patients may be hospitalized for treatment and disability may occur.

Risk factors and risk groups:

The denosumab development program comprises studies of older subject populations (e.g., osteoporosis, cancer) that are likely to have a higher incidence of pre-existing cardiovascular conditions and, thus, a higher incidence of cardiovascular toxicities than that of the general population [15; 23].

Risk factors for atherosclerosis include age, sex, ethnicity, family history, elevated lipid levels, cigarette smoking, hypertension, diabetes, and concomitant medications, including antipsychotic agents and COX-2 inhibitors [21; 25]

Preventability:

No preventive measures are known.

Impact on the risk-benefit balance of the product:

The potential risk of cardiovascular events has been considered in overall assessment supporting a positive benefit-risk profile.

Public health impact:

Significant public health impact of Prolia® on cardiovascular disease severity or incidence is not anticipated.

SVII.3.1.2. Malignancy

Potential mechanism(s):

RANK ligand is expressed on activated T and B cells and in the lymph nodes and some reports have described immune modulatory effects of RANKL inhibition; however, in vitro studies of RANK and RANKL activity on a wide range of human tumor types provide no evidence for carcinogenic risk associated with RANKL inhibition [7; 18]. In in vivo rodent cancer models, RANKL inhibition has been shown to have a beneficial effect [8; 10; 27; 29; 30]

If denosumab did affect immune function, a hypothetical association with malignancies linked to immune modulation could exist and would be expected to show the pattern of malignancy associated with immune deficiency.

Evidence source(s) and strength of evidence:

This is considered a potential risk based on theoretical concerns and has not been substantiated in the extensive clinical study program or in the postmarketing experience.

Characterisation of the risk:

Frequency

In the large pivotal PMO study (20030216) from Prolia®, the subject incidence of new primary malignancy was 4.8% with denosumab and 4.3% with placebo (HR [95% CI] = 1.11 [0.90, 1.37]).

In the pivotal HALT prostate cancer study (20040138) from Prolia®, the subject incidence of new primary malignancy was 5.1% with denosumab and 4.6% with placebo (HR [95% CI] = 1.08 [0.67, 1.72]), and overall survival was 94.1% in each treatment group (HR [95% CI] = 0.99 [0.65, 1.52]).

During the placebo-controlled phase of the MOP study from Prolia®, 4 subjects in the denosumab group (3.3%) and no subject in the placebo group reported events of malignancy. The events were prostate cancer in 3 subjects and basal cell carcinoma in 1 subject. Two prostate cancer cases were likely present at baseline based on past medical history.

In the 24-month final analysis of the GIOP study from Prolia®, subject incidence of malignancy was 3.0% with denosumab and 1.8% with risedronate (HR [95% CI] = 1.75 [0.69, 4.44]). Subject incidence of serious adverse events of malignancy was 1.8% with denosumab and 1.6% with risedronate.

Severity

Malignancy is a clinically important event requiring medical intervention.

Reversibility

Although some malignancies will respond to treatment, long-term survival will depend upon multiple factors and as such onset of malignancy is rarely considered reversible.

Long-term outcomes

New primary malignancy or progression of existing malignancy may be fatal, life-threatening, and long-term outcomes will likely be impacted.

Impact on quality of life

Malignancy can be life-threatening and generally requires intervention e.g., surgery, radiation, and/or chemotherapy.

Risk factors and risk groups:

General factors far risk of malignancy include advancing age, diet, cigarette smoking, excessive ethanol consumption, and numerous environmental toxins. In addition, cancer populations are at increased risk for a second primary malignancy because of their existing malignancy, possible genetic predisposition, and exposure to chemotherapy and radiation treatment [6]

Preventability:

No preventive measures are known.

Impact on the risk-benefit balance of the product:

The potential risk of malignancy has been considered in the product benefit-risk assessment which supports a positive benefit-risk profile in the indicated populations.

Public health impact:

Significant public health impact is not anticipated.

SVII.3.2 Presentation of the Missing Information

There is no missing information for ZADENVI (denosumab).

PART II: Module SVIII - Summary of safety concerns

Table 12. Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Hypocalcemia • Skin infection leading to hospitalisation • Osteonecrosis of the jaw • Hypersensitivity reactions • Atypical femoral fracture • Hypercalcemia in pediatric patients receiving Denosumab and after treatment discontinuation
Important potential risks	• Fracture healing complications • Infection • Cardiovascular events • Malignancy
Missing information	• None

PART III: Pharmacovigilance plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection are presented in Table 10.

Table 13. Specific Adverse Reaction Follow-up Questionnaires

Follow-up Questionnaire (Annex 4)	Safety Concern(s)	Purpose
Hypocalcemia	Hypocalcemia	To monitor the nature of hypocalcemia in patients treated with denosumab in the postmarketing environment.
Infection	Skin infection leading to hospitalisation Infection	To monitor the nature of skin infections leading to hospitalisation and infections of any type reported in patients treated with denosumab in the postmarketing environment.
Osteonecrosis of the jaw	Osteonecrosis of the jaw	To monitor the nature of ONJ in patients treated with denosumab in the postmarketing environment.
Postmarketing reports of potential atypical fracture	Atypical femoral fracture	To monitor the nature of AFF reported in patients treated with denosumab in the postmarketing environment.
Fracture healing	Fracture healing complications	To monitor the nature of fracture healing complications reported in patients treated with denosumab in the postmarketing environment.
Malignancy	Malignancy	To monitor the nature of malignancy adverse events reported in patients treated with denosumab in the postmarketing environment.
Hypersensitivity	Hypersensitivity reactions	To monitor the nature of hypersensitivity reported in patients treated with denosumab in the postmarketing environment.

III.2 Additional pharmacovigilance activities

The pharmacovigilance plan does not include any additional pharmacovigilance activities.

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 14. Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Important Identified Risks	
Hypocalcemia	Routine risk communication: • SmPC Section 4.2, 4.3, 4.4, and 4.8 • Package leaflet (PL) Section 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendation for correction of hypocalcemia prior to initiating treatment with ZADENVI and clinical monitoring of calcium levels during treatment with ZADENVI is included in SmPC Section 4.4.
Skin infection leading to hospitalisation	Routine risk communication: • SmPC sections 4.4 and 4.8 • PL sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • None
Osteonecrosis of the jaw	Routine risk communication: • SmPC sections 4.4 and 4.8 • PL sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendation for oral examination, maintenance of good oral hygiene during treatment, management of patients with unavoidable invasive dental procedures, and temporary interruption of treatment if ONJ occurs is included in SmPC Section 4.4.
Hypersensitivity reactions	Routine risk communication: • SmPC sections 4.3 and 4.8 • PL sections 2 and 4

Safety concern	Routine risk minimisation activities
Important Identified Risks	
	Routine risk minimisation activities recommending specific clinical measures to address the risk: • None
Atypical femoral fracture	Routine risk communication: • SmPC Section 4.4 and 4.8 • PL Section 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendation for reporting new or unusual thigh, hip, or groin pain is included in SmPC Section 4.4.
Hypercalcemia in pediatric patients receiving denosumab and after treatment discontinuation	Routine risk communication: • SmPC sections 4.2, 4.4 and 4.8 • PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: • None
Important Potential Risks	
Fracture healing complications	Routine risk communication: • SmPC Section 5.3 Routine risk minimisation activities recommending specific clinical measures to address the risk: • None
Infection	Routine risk communication: • SmPC section 4.8 • PL section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • None
Cardiovascular events	Routine risk communication: • None Routine risk minimization activities recommending specific clinical measures to address the risk: • None
Malignancy	Routine risk communication: None

Safety concern	Routine risk minimisation activities
Important Identified Risks	
	Routine risk minimization activities recommending specific clinical measures to address the risk: None
Missing Information	
None	

V.2 Additional risk minimisation measures

Patient Reminder Card

Objectives	Patient reminder cards will be provided to address the following risk: • Osteonecrosis of the jaw
Rationale for the additional risk minimization activity	The purpose of the patient reminder card is to remind patients about important safety information that they need to be aware of before and during treatment with denosumab (ZADENVI) injections for osteoporosis and bone loss, including: • the risk of osteonecrosis of the jaw during treatment with ZADENVI; • the need to highlight any problems with their mouth or teeth to their doctors/nurses before starting treatment; • the need to ensure good oral hygiene during treatment and receive routine dental check-ups; • the need to inform their dentist of treatment with ZADENVI and to contact their doctor or dentist immediately if problems with the mouth or teeth occur during treatment.
Target audience and planned distribution path	Target audience will be the patients. The patient reminder card is distributed to prescribers with instruction to provide it to patients. The patient reminder card is distributed by mail and prescribers are provided with contact details to request additional copies of the card. Some national plans include making the patient reminder card available on a website.
Plans to evaluate the effectiveness of the interventions and criteria for success	Monitor and evaluate postmarketing and clinical study safety data and report in periodic safety updated reports (PSURs). The distribution of the patient reminder card will be tracked to ensure that it is distributed in accordance with the plan agreed with national agencies. Additional requests for patient reminder cards and web downloads will also be recorded as an indicator of ongoing use of the patient reminder card. The effectiveness of risk minimization of ONJ in the EU will be monitored through postmarketing reporting rates of ONJ before and after introduction of the patient reminder card compared to the rest of the world. In addition, the focused questionnaire for postmarketing reports of ONJ presented in Annex 4. Specific Adverse Drug Reaction Follow-up Forms will be revised to permit inclusion of data on whether the patient affected by ONJ had previously received a patient reminder card or not.

Evaluation of the effectiveness of the risk minimization activities	No change in risk-benefit profile

V.3 Summary of risk minimisation measures

Table 12. Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Important Identified Risks		
Hypocalcemia	Routine risk minimisation measures: • SmPC section 4.4 where recommendation regarding correction and monitoring of calcium levels is provided. • SmPC Section 4.2, 4.3 and 4.8. • PL sections 2 and 4 Additional risk minimization measures • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire for hypocalcemia Additional pharmacovigilance activities: • None
Skin infection leading to hospitalisation	Routine risk minimisation measures: • SmPC Section 4.4 and 4.8 • PL Section 2 and 4 Additional risk minimization measures • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire for infection Additional pharmacovigilance activities: • None
Osteonecrosis of the jaw	Routine risk minimisation measures: • SmPC sections 4.4 where oral hygiene and dental management guidance is provided. • SmPC Section 4.8 • PL Section 2 and 4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire for ONJ

	Additional risk minimization measures: • Patient reminder card	• External adjudication of events reported in clinical trials. • Independent medical review of postmarketing study reports. Additional pharmacovigilance activities: • None
Hypersensitivity reactions	Routine risk minimisation measures: • SmPC sections 4.3 and 4.8 • PL sections 2 and 4 Additional risk minimization measures • None	Routine pharmacovigilance beyond adverse reactions reporting and signal detection: • Follow-up questionnaire for hypersensitivity Additional pharmacovigilance activities: • None
Atypical femoral fracture	Routine risk minimisation measures: • SmPC section 4.4, where recommendation for reporting potential symptoms is provided. • SmPC Section 4.8 • PL Section 2 and 4 Additional risk minimization measures • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire for AFF • External adjudication of clinical trial cases • Independent medical review of postmarketing study reports Additional pharmacovigilance activities: • None

Hypercalcemia in pediatric patients receiving denosumab and after treatment discontinuation	Routine risk minimisation measures: • SmPC sections 4.2, 4.4 and 4.8 • PL section 2 Additional risk minimization measures • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities • None

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Important Potential Risks		
Fracture healing complications	Routine risk minimisation measures: • SmPC Section 5.3 Additional risk minimization measures • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire for fracture healing complications Additional pharmacovigilance activities: • None
Infection	Routine risk minimisation measures: • SmPC section 4.8 • PL section 4 Additional risk minimization measures • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire for infection Additional pharmacovigilance activities: • None
Cardiovascular events	Routine risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse

	Additional risk minimization measures • None	reactions reporting and signal detection: • None Additional pharmacovigilance activities • None
Malignancy	Routine risk minimisation measures: • None Additional risk minimization measures • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire for Malignancy Additional pharmacovigilance activities: • None

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Missing Information		
None		

PART VI: Summary of the risk management plan

Summary of risk management plan for ZADENVI (denosumab)

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

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

This summary of the RMP for ZADENVI 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 ZADENVI RMP.

I. The medicine and what it is used for

ZADENVI is authorised for the treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures, the treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures, and treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture (see SmPC for the full indication). It contains denosumab as the active substance and it is given by subcutaneous injection.

Further information about the evaluation of ZADENVI benefits can be found in ZADENVI EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <Pre-authorisation RMP (this line should be only edited by EMA): link to the EPAR summary landing page>.

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

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

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 authorized 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 public (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

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

In addition to these measures, information about adverse events is collected continuously and regularly analyzed, including periodic safety update report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of ZADENVI is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of ZADENVI are risks that need special risk management activities to further investigate a minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified a potential. Identified risks are concerns for which there is sufficient proof of a link with the use of ZADENVI. Potential risks are concerns far 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	• Hypocalcemia • Skin infection leading to hospitalisation • Osteonecrosis of the jaw • Hypersensitivity reactions • Atypical femoral fracture • Hypercalcemia in Pediatric Patients Receiving Denosumab and after treatment discontinuation
Important potential risks	• Fracture healing complications • Infection • Cardiovascular events • Malignancy
Missing information	• None

II.B Summary of important risks

Important Identified risk 1: Hypocalcemia	
Evidence for linking the risk to the medicine	This risk was identified in the phase III, randomized, double-blind, placebo- or active-controlled studies
Risk factors and risk groups	Risk factors include severe renal impairment and hyperphosphatemia. Other risks factors may include a history of hypoparathyroidism, parathyroid hormone resistance, vitamin D deficiency or resistance, thyroid surgery, parathyroid surgery, malabsorption syndromes, excision of small intestine, severe renal impairment (creatinine clearance < 30 mL/min), dialysis, and some medications [12]
Risk minimisation measures	Routine risk minimization measures: • SmPC Section 4.4, where recommendation regarding correction and monitoring of calcium levels is provided • SmPC Section 4.2, 4.3, and 4.8 • PL Section 2 and 4 Additional risk minimization measures: • None
Additional pharmacovigilance activities:	None.

Important Identified risk 2: Skin infection leading to hospitalisation	
Evidence for linking the risk to the medicine	This risk was identified in the phase 3, randomized, double-blind, placebo- or active-controlled studies.
Risk factors and risk groups	Risk factors for infection in general include increasing age, immunosuppression associated with cancer, diabetes, human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), immunosuppressant drugs (e.g., corticosteroids, arthritis medications, and chemotherapy drugs), substance abuse, and malnutrition. Risk factors for skin infection in older patients include skin wounds, peripheral vascular disease, eczema/dermatitis, and venous stasis disorders.
Risk minimisation measures	Routine risk minimization measures: • SmPC Section 4.4, and 4.8 • PL Section 2 and 4

	Additional risk minimization measures: • None
Additional pharmacovigilance activities:	None.

Important Identified risk 3: Osteonecrosis of the jaw	
Evidence for linking the risk to the medicine	This risk was identified in open-label long-term extensions to phase III, randomized, double-blind, placebo-controlled studies.
Risk factors and risk groups	Risk factors include duration of exposure to denosumab, prior bisphosphonate use (particularly for extended periods of time), older age, periodontal disease, dentoalveolar surgery, trauma from poorly fitting dentures, malignancy, chemotherapy, corticosteroids, smoking, systemic or regional infection, immune-compromised state predisposing to increased risk of infection, hypercoagulable state secondary to underlying malignancy, and vascular insufficiency due to thrombosis [18; 22]
Risk minimisation measures	Routine risk minimization measures: • SmPC Section 4.4, where oral hygiene and dental management guidance is provided • SmPC Section 4.8 • PL Section 2 and 4 Additional risk minimization measures: • Patient reminder card
Additional pharmacovigilance activities:	None.

Important Identified risk 4: Hypersensitivity reactions	
Evidence for linking the risk to the medicine	This risk was identified in the postmarketing setting based on a clinically plausible association between administration of denosumab and hypersensitivity events.
Risk factors and risk groups	Known hypersensitivity to denosumab and any of its excipients.
Risk minimisation measures	Routine risk minimization measures: • SmPC Section 4.3 and 4.8 • PL Section 2 and 4

	Additional risk minimization measures: • None
Additional pharmacovigilance activities:	None.

Important Identified risk 5: Atypical Femoral Fracture	
Evidence for linking the risk to the medicine	This risk was identified in an open-label long-term extension to a phase III, randomized, double-blind, active-controlled study.
Risk factors and risk groups	Long-term antiresorptive treatment has been associated with atypical femoral fracture. Corticosteroids have also been reported in the literature to potentially be associated with atypical femoral fracture [14;19] Atypical femoral fractures have also been reported in patients with certain comorbid conditions (eg, vitamin D deficiency, rheumatoid arthritis, hypophosphatasia) and with use of bisphosphonates, glucocorticoids, and proton pump inhibitors [24]
Risk minimisation measures	Routine risk minimization measures: • SmPC Section 4.4, where recommendation for reporting potential symptoms is provided. • SmPC Section 4.8 • PL Section 2 and 4 Additional risk minimization measures: • None
Additional pharmacovigilance activities:	None.

Important Identified risk 6: Hypercalcemia in Pediatric Patients Receiving Denosumab and after treatment discontinuation	
Evidence for linking the risk to the medicine	Data to evaluate safety concerns derived from Prolia® clinical trials in pediatric subjects with osteogenesis imperfecta, XGEVA® clinical studies and postmarketing adverse event reporting involving pediatric patients receiving denosumab at unapproved doses and/or unapproved indications for use.

Risk factors and risk groups	Pediatric patients with growing skeletons and high bone turnover disease states (such as osteogenesis imperfecta).
Risk minimisation measures	Routine risk minimization measures: • SmPC Section 4.2, 4.4 and 4.8 • PL Section 2 Additional risk minimization measures: • None
Additional pharmacovigilance activities	None.

Important potential risk 1: Fracture healing complications	
Evidence for linking the risk to the medicine	This is a theoretical risk based on the potential mechanism of action.
Risk factors and risk groups	General risk factors for fracture healing complications are thought to include older age, diabetes, use of medications such as non-steroidal anti-inflammatory drugs and corticosteroids, smoking, excessive alcohol use, and poor nutrition [13; 16]
Risk minimisation measures	Routine risk minimization measures: • SmPC Section 5.3 Additional risk minimization measures: • None
Additional pharmacovigilance activities:	None.

Important potential risk 2: Infection	
Evidence for linking the risk to the medicine	This is considered a potential risk based on theoretical concerns which has not been substantiated in the extensive clinical study program or in the postmarketing experience.
Risk factors and risk groups	Risk factors for infection in general include increasing age, immunosuppression associated with cancer, diabetes, HIV/AIDS, immunosuppressant drugs (e.g., corticosteroids, arthritis medications, and chemotherapy drugs), substance abuse, and malnutrition.
Risk minimisation measures	Routine risk minimization measures:

	• SmPC Section 4.8 • PL Section 4 Additional risk minimization measures: • None
Additional pharmacovigilance activities:	None.

Important potential risk 3: Cardiovascular events	
Evidence for linking the risk to the medicine	This is a theoretical risk based on epidemiological data demonstrating elevated osteoprotegerin in patients with cardiovascular disease.
Risk factors and risk groups	The denosumab development program comprises studies of older subject populations (e.g., osteoporosis, cancer) that are likely to have a higher incidence of pre-existing cardiovascular conditions and, thus, a higher incidence of cardiovascular toxicities than that of the general population [15;23]. Risk factors for atherosclerosis include age, sex, ethnicity, family history, elevated lipid levels, cigarette smoking, hypertension, diabetes, and concomitant medications, including antipsychotic agents and COX-2 inhibitors (Murphy and Dargie, Drug Safety, 2007;30(9):783-804; Smith et al, Circulation, 2004;109{21):2613-2616).
Risk minimisation measures	Routine risk minimization measures: • None Additional risk minimization measures: • None
Additional pharmacovigilance activities:	• None

Important potential risk 4: Malignancy	
Evidence for linking the risk to the medicine	This is considered a potential risk based on theoretical concerns and has not been substantiated in the extensive clinical study program or in the postmarketing experience.
Risk factors and risk groups	General factors for risk of malignancy include advancing age, diet, cigarette smoking, excessive ethanol consumption, and

	numerous environmental toxins. In addition, cancer populations are at increased risk for a second primary malignancy because of their existing malignancy, possible genetic predisposition, and exposure to chemotherapy and radiation treatment (Anand et al, Pharm Res. 2008; 25(9):209-72116; World Health Organization, Global Status Report on Noncommunicable Diseases 2010, http://www.who.int)
Risk minimisation measures	Routine risk minimization measures: • None Additional risk minimization measures: • None
Additional pharmacovigilance activities:	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 authorisation or specific obligation of ZADENVI.

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

There are no studies required for ZADENVI.

Annex 4 - Specific adverse drug reaction follow-up forms

Table of Contents

Follow-up Form Title	Version Number	Date of Follow-up Version
Hypocalcemia	-	29-Oct-2024
Infection	-	29-Oct-2024
Osteonecrosis of the jaw	-	29-Oct-2024
Postmarketing reports of potential atypical fracture	-	29-Oct-2024
Fracture healing	-	29-Oct-2024
Malignancy	-	29-Oct-2024
Hypersensitivity	-	29-Oct-2024

DENOSUMAB Core Questionnaire
Fracture healing

AE Case ID #

This form is subject to applicable laws governing the protection of personal information. The information provided on this form is collected for pharmacovigilance purposes, may be transferred, and processed outside of the country in which it is collected. mAbxience does not wish to receive information through which a patient can be identified therefore do not provide any information other than the specific information required by this form. This prohibition includes, for example, name, address, telephone number and government issued identifier.

PATIENT/CASE ADMINISTRATIVE INFORMATION (Please indicate dates as DD/MM/YYYY)

Patient Identifier

Patient Initials

Date of Event Onset

Date of this report

Gender: ☐ Male ☐ Female Weight:_____Ib _____Kg

Age at the time of event: _____

Event Reported Term

Study No.

Safety Database No.

☐ Clinical Trial
☐ Post- marketing

DENOSUMAB ADMINISTRATION/INFORMATION (Please indicate dates as DD/MM/YYYY)

Denosumab indication:

☐ Postmenopausal osteoporosis

☐ Bone loss from hormone ablation therapy
Please specify diagnosis _____
_____

☐ Advanced cancer with bone metastasis
Please specify cancer_____

☐ Other (please specify)_____
_____

☐ Don't know

Denosumab Dose:

☐ 60 mg SC every 6 months ☐ 120 mg SC every 4 weeks

☐ Other (please specify)_____

☐ Don't know

Denosumab Exposure:

Denosumab first administered (date)_____ (study#)_____

Last denosumab dose before event (date)_____

Doses of denosumab were skipped ☐ Yes ☐ No ☐ Unknown
If yes, please specify_____

Doses of denosumab given after event began ☐ Yes ☐ No ☐ Unknown
If yes, date of first dose following star of event _____

DIAGNOSIS (Check all that apply, please indicate dates as DD/MM/YYYY)

Date of fracture: _____ Date of fracture delayed healing: _____ Date of fracture non-healing: _____

☐ **Fracture to upper body (i.e., above waist)**
Specify location (check all that apply):

- ☐ Cervical spine
- ☐ Clavicle
- ☐ Hand/metacarpal/phalange
- ☐ Head/face/skull
- ☐ Humerus
- ☐ Olecranon
- ☐ Wrist/carpal
- ☐ Radius
- ☐ Rib
- ☐ Scapula
- ☐ Shoulder
- ☐ Sternum
- ☐ Ulna
- ☐ Other _____

☐ **Fracture to lower body (i.e., below waist)**
Specify location (check all that apply):

- ☐ Ankle
- ☐ Femur (please specify location: neck, subtrochanteric, mid shaft, etc.)
_____
- ☐ Hip
- ☐ Patella
- ☐ Pelvis
- ☐ Tibia
- ☐ Fibula
- ☐ Foot/tarsal/metatarsal/phalange
- ☐ Other _____

Type of trauma reported at time of fracture (check one):

- ☐ Severe trauma (e.g., falling from roof, motor vehicle accident)
- ☐ Minimal trauma (e.g., falling from standing position or less)
- ☐ Non-traumatic

Characteristics of fracture (check all that apply):

- ☐ Comminuted
- ☐ Compound
- ☐ Pathologic
- ☐ Poor alignment
- ☐ Poor immobilization of segments
- ☐ Soft tissue injury
- ☐ Unknown

DENOSUMAB Core Questionnaire
Fracture healing (continued)

AE Case ID #

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PATIENT/CASE ADMINISTRATIVE INFORMATION (Please indicate all dates as DD/MM/YYYY)

Patient Identifier

Patient Initials

Safety Database No.

TREATMENT (Please provide dates and indicate attachments if available)

Methods to reduce and set fracture (check all that apply):

☐ Casting _____ ☐ Surgery _____

☐ Non-surgical reduction _____ ☐ Traction _____

☐ Revision surgery (2nd surgery) _____ ☐ Other _____

Did the fracture heal (union)? ☐ Yes ☐ No ☐ Unknown

If yes, provide date of union (DD/MM/YYYY): _____

If yes, was healing confirmed through imaging? ☐ Yes ☐ No ☐ Unknown

If yes, what diagnostic imaging (check all that apply): ☐ X-rays ☐ CT scans ☐ MRI

If yes, is patient able to walk without assistance? ☐ Yes ☐ No ☐ Unknown

MEDICAL HISTORY/RISK FACTORS (Check all that apply, provide dates and attach relevant reports)

☐ Current smoker/tobacco use

_____

_____

☐ History or current corticosteroid use

_____

_____

☐ Prior fracture history

_____

_____

☐ Diabetes

_____

_____

REPORTER

Name:
Address:
City: State:
Country: Province:
Email: Postal Code:
Phone (include country code):

Signature_____

Title_____ **Date**_____

E-mail address:

DENOSUMAB Core Questionnaire Hypersensitivity

AE Case ID #

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PATIENT/CASE ADMINISTRATIVE INFORMATION (Please indicate dates as DD/MM/YYYY)

Patient Identifier

Patient Initials

Date of Event Onset

Date of this report

Gender: ☐ Male ☐ Female Weight:_____lb _____Kg

Age at the time of event: _____

Event Reported Term

Study No.

Safety Database No.

☐ Clinical Trial
☐ Post- marketing

DENOSUMAB ADMINISTRATION/INFORMATION (Please indicate dates as DD/MM/YYYY)

Denosumab indication

☐ Postmenopausal osteoporosis

☐ Bone loss from hormone ablation therapy
Please specify diagnosis _____
_____

☐ Advanced cancer with bone metastasis
Please specify cancer

☐ Other
Please specify_____
_____

☐ Don't know

☐ **Denosumab Antibody Testing Performed**: (provide dates and results_
If not performed, do you have interest in antibody testing? ☐ Yes ☐ No

Denosumab Dose

☐ 60 mg SC every 6 months ☐ 120 mg SC every 4 weeks

☐ Other Please specify_____

☐ Don't know

Denosumab Exposure:

Denosumab first administered (date)_____

Last denosumab dose before event (date)

☐ Doses of denosumab were skipped ☐ Yes ☐ No ☐ Unknown
If yes, please specify_____

☐ Doses of denosumab given after event began ☐ Yes ☐ No ☐ Unknown
If yes, date of first dose following star of event _____

_____

_____

SIGNS AND SYMPTOMS (Check all that apply)

☐ Anaphylaxis	☐ Facial edema	☐ Rash	☐ Diarrhea	☐ Tachycardia	☐ Other (specify)
☐ Angioneurotic edema	☐ Hypotension	☐ Shortness of breath	☐ Pruritis	☐ Urticaria	_____
☐ Colic	☐ Laryngeal edema	☐ Stridor	☐ Swelling	☐ Wheezing	_____

EVALUATIONS, DIAGNOSIS & LABORATORY MEASURES (Please indicate and attach copy of report if available)

Diagnostic	Results/ Units	Reference Range/Units	Date	Report Attached Y / N
Results at BASELINE (prior to mAxience drug)				
CBC with Differential				
WBC				
RBC				
Eosinophils				
Hgb				
Hct				
Platelets				
Other				
Albumin				
Total Protein				
BUN				
Serum Creatinine				
ALT				
AST				
ALP				
Bilirubin				
Calcium				
K+				
Na+				
Phosphorus				
Mg++				
Cl-				
CrCl				

Diagnostic	Results/ Units	Reference Range/Units	Date	Report Attached Y / N
Results at TIME OF EVENT				
CBC with Differential				
WBC				
RBC				
Eosinophils				
Hgb				
Hct				
Platelets				
Other				
Albumin				
Total Protein				
BUN				
Serum Creatinine				
ALT				
AST				
ALP				
Bilirubin				
Calcium				
K+				
Na+				
Phosphorus				
Mg++				
Cl-				
CrCl				

DENOSUMAB Core Questionnaire Hypersensitivity (continued)

AE Case ID #

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PATIENT/CASE ADMINISTRATIVE INFORMATION (Please indicate dates as DD/MM/YYYY)

Patient Identifier

Patient Initials

Safety Database No.

TREATMENT (Please provide dates and indicate attachments if available)

☐ ER corticosteroids

Route: ☐ IV only ☐ oral

☐ ER anti-histaminics

Route: ☐ IV only ☐ oral only ☐ both oral and IV

☐ Required hospital admission ☐ Yes ☐ No

Overall length of hospital stay

☐ < 1 day ☐ > 1 day or < 7 days ☐ > 7 days

☐ ICU admission ☐ Yes ☐ No ☐ Unknown

Overall length of hospital stay

☐ < 1 day ☐ > 1 day or < 7 days ☐ > 7 days

☐ In-hospital corticosteroids

Route: ☐ IV only ☐ oral only ☐ both oral and IV

☐ In-hospital anti-histaminics

Route: ☐ IV only ☐ oral only ☐ both oral and IV

☐ Other in-hospital treatment

☐ IV vasopressors ☐ Yes ☐ No ☐ Unknown

☐ Intubation/mechanical ventilation ☐ Yes ☐ No ☐ Unknown

☐ Hospital admission/discharge report (please attach if available)

_____

_____

_____

_____

_____

_____

_____

CONCOMITANT MEDICATION

☐ ACE inhibitors

☐ Allopurinol

☐ Cancer chemotherapy

☐ Dapsone

☐ IV contrast

☐ NSAIDS/aspirin

☐ Penicillamine

☐ Rifampin

☐ Anticonvulsants (check with apply):

- ☐ Phenytoin
- ☐ Carbamazepine
- ☐ Phenobarbital

☐ Antibiotics (check with apply):

- ☐ Beta-lactams including penicillin and cephalosporin
- ☐ Macrolides
- ☐ Sulfonamides
- ☐ Quinolones

☐ Hypersensitivity event resolved ☐ Yes ☐ No ☐ Unknown

If yes, date (DD/MM/YYYY):_____

☐ Final diagnosis or etiology (incl, start date). Please send supporting document for diagnosis _____

☐ Other consult report (please indicate any attachments _____

_____

_____

_____

E-mail address:

REPORTER

Name:

Address:

City:

Country:

Email:

Phone (Include country code)

State:

Province:

Postal Code:

Signature_____

Title_____ **Date**_____

DENOSUMAB Core Questionnaire
Hypocalcemia

AE Case ID #

This form is subject to applicable laws governing the protection of personal information. The information provided on this form is collected for pharmacovigilance purposes, may be transferred, and processed outside of the country in which it is collected. mAbxience does not wish to receive information through which a patient can be identified therefore do not provide any information other than the specific information required by this form. This prohibition includes, for example, name, address, telephone number and government issued identifier.

PATIENT/CASE ADMINISTRATIVE INFORMATION (Please indicate dates as DD/MM/YYYY)

Patient Identifier

Patient Initials

Date of Event Onset

Date of this report

Gender: ☐ Male ☐ Female Weight:_____lb _____Kg

Age at the time of event: _____

Event Reported Term

Study No.

Safety Database No.

☐ Clinical Trial
☐ Post- marketing

DENOSUMAB ADMINISTRATION/INFORMATION (Please indicate dates as DD/MM/YYYY)

Denosumab indication

☐ Postmenopausal osteoporosis

☐ Bone loss from hormone ablation therapy
Please specify diagnosis _____
_____

☐ Advanced cancer with bone metastasis
Please specify cancer

☐ Other
Please specify_____
_____

☐ Don't know

Denosumab Dose

☐ 60 mg SC every 6 months ☐ 120 mg SC every 4 weeks

☐ Other Please specify_____

☐ Don't know

Denosumab Exposure

Denosumab first administered (date)_____

Last denosumab dose before event (date)

☐ Doses of denosumab were skipped ☐ Yes ☐ No ☐ Unknown
If yes, please specify_____

☐ Doses of denosumab given after event began ☐ Yes ☐ No ☐ Unknown
If yes, date of first dose following start of event _____

SIGNS AND SYMPTOMS (Check all that apply)

☐ Numbness
(Specify if involving digits and/or peri-oral region) _____

☐ Convulsions ☐ Muscle twitching

☐ Muscle cramping ☐ Paresthesia

☐ Syncope ☐ Tetany

☐ None ☐ Other _____

DIAGNOSIS (Check all that apply)

Serum calcium at time of event: _____mg/dl ☐ Unknown

Please provide serum albumin result _____

Serum albumin at the time of event < 4.0g/dl?
☐ Yes ☐ No ☐ Unknown

If yes, what were the ionized calcium levels? _____ mmol/dL

Serum creatinine at time of event was > 2.0 X times upper limit of normal?
(Please provide result) _____ ☐ Yes ☐ No ☐ Unknown

Hypocalcemia-induced EKG changes (QT prolongation)?
☐ Yes ☐ No ☐ Unknown

TREATMENT

Treatment only as an outpatient? ☐ Yes ☐ No

If yes, route of calcium replacement: ☐ IV ☐ Oral ☐ Unknown

Treated in the ER? ☐ Yes ☐ No

If yes, route of calcium replacement: ☐ IV ☐ Oral ☐ Unknown

Treatment included general hospital admission for calcium replacement?
☐ Yes ☐ No ☐ Unknown

If yes, route of calcium replacement: ☐ IV ☐ Oral ☐ Unknown

Treatment included ICU admission? ☐ Yes ☐ No ☐ Unknown

If yes, route of calcium replacement: ☐ IV ☐ Oral ☐ Unknown

Overall length of hospital stay:
☐ ≤1day ☐ >1day ☐ ≤7days ☐ >7 days

Anti-arrhythmic medications? ☐ Yes ☐ No ☐ Unknown

If yes, please provide the details such as names and dates of treatment
Anti-arrhythmic medications _____

Other treatment? ☐ Yes ☐ No ☐ Unknown

If yes, specify: _____

E-mail address:

REPORTER

Name:

Address:
City:
Country:

State:
Province:
Postal Code:

Email:

Phone: (include country code)

Signature_____

Title_____ **Date**_____

DENOSUMAB Core Questionnaire
Hypocalcemia (continued)

AE Case ID #

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PATIENT/CASE ADMINISTRATIVE INFORMATION (Please indicate dates as DD/MM/YYYY)

Patient Identifier | Patient Initials | Safety Database No.

RISK FACTORS (Check all that apply)

Medical History Risk Factors

Does the patient have any of the following risk factors:	☐ YES ☐ NO	If yes, please provide dates and details
☐ Acute pancreatitis	☐ History of chronic renal disease	
☐ History of parathyroid disease	☐ History of hypoalbuminemia	
☐ History of malignancy (please specify)	☐ Hypoproteinemia	
☐ Hyperphosphatemia	☐ Magnesium deficiency	
☐ Recent surgery	☐ Sepsis	

☐ Vitamin D deficiency (if patient has a history of vitamin D deficiency, were the vitamin D levels normal at the time of event?

Please provide the vitamin D levels at the time of the hypocalcemia event.

☐ Prior hypocalcemia event (before denosumab treatment)

Please provide dates and details of prior hypocalcemia event

Medical Risk Factors

Antineoplastic agents? (Check which apply): ☐ cisplatin ☐ cytosine arabinoside ☐ Other_____ ☐ None

Antimicrobials? (Check which apply): ☐ pentamidine ☐ ketoconazole ☐ Other_____ ☐ None

Concomitant Medications

Taking vitamin D supplement? (Check which apply): ☐ YES ☐ NO ☐ Unknown (Please provide dose and dates)

Taking calcium supplement? (Check which apply): ☐ YES ☐ NO ☐ Unknown (Please provide dose and dates)

Other concomitant medications

Hypocalcemic event resolved ☐ YES ☐ NO ☐ Unknown

If yes, what date? (DD/MM/YYYY)_____

REPORTER

Name:
Address:
City: State:
Country: Province:
Email: Postal Code:
Phone (Included country code)
Signature_____
Tittle_____ **Date**_____

E-mail address:

DENOSUMAB Core Questionnaire
Infection

AE Case ID #

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PATIENT/CASE ADMINISTRATIVE INFORMATION (Please indicate dates as DD/MM/YYYY)

Patient Identifier

Patient Initials

Date of Event Onset

Date of this report

Gender: ☐ Male ☐ Female Weight:_____Ib _____Kg

Event Reported Term

Age at the time of event: _____

Study No.

Safety Database No.

☐ Clinical Trial
☐ Post- marketing

DENOSUMAB ADMINISTRATION/INFORMATION (Please indicate dates as DD/MM/YYYY)

Denosumab indication

☐ Postmenopausal osteoporosis

☐ Bone loss from hormone ablation therapy
Please specify diagnosis _____
_____

☐ Advanced cancer with bone metastasis
Please specify cancer

☐ Other
Please specify_____
_____

☐ Don't know

Denosumab Dose

☐ 60 mg SC every 6 months ☐ 120 mg SC every 4 weeks

☐ Other Please specify_____

☐ Don't know

Denosumab Exposure

Denosumab first administered (date)_____

Last denosumab dose before event (date) _____

☐ Doses of denosumab were skipped ☐ Yes ☐ No ☐ Unknown
If yes, please specify_____

☐ Doses of denosumab given after event began ☐ Yes ☐ No ☐ Unknown
If yes, date of first dose following star of event _____

SIGNS AND SYMPTOMS (Check all that apply, provide dates of onset, resolution, if available)

☐ Fever _____
☐ Cough _____
☐ Swelling _____
Location _____
☐ Shortness of breath
_____

☐ Pain _____
Location _____
☐ Rash _____
Location _____
☐ Prolonged fatigue _____
☐ Diarrhea _____

☐ Discharge _____
Location _____
Description_____
☐ Chills _____
☐ Night sweats_____
☐ Other_____

☐ Organ system affected:
☐ Cardiac
☐ Ear/nose
☐ Throat
☐ Gastrointestinal
☐ Respiratory

☐ Musculoskeletal (including joints)
☐ Nervous (cerebrospinal fluid)
☐ Skin Location _____
☐ Kidney/genito-urinary
☐ Systemic (bacteremia and/or sepsis)
☐ Other _____

EVALUATIONS, DIAGNOSIS & LABORATORY MEASURES (Please attach copy of report)

Diagnostic	Results/Units	Reference Range/Units	Date	Report Attached	
				Y	N

Diagnostic	Results/Units	Reference Range/Units	Date	Report Attached	
				Y	N

DENOSUMAB Core Questionnaire
Infection (continued)

AE Case ID #

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PATIENT/CASE ADMINISTRATIVE INFORMATION (Please indicate dates as DD/MM/YYYY)

Patient Identifier

Patient Initials

Safety Database No.

SIGNS AND SYMPTOMS (Check all that apply, provide dates of onset, resolution, if available)

CHECK WHICH INFECTION APPLIES

☐ Cardiac infections
- ☐ Endocarditis_____
- ☐ Pericarditis (purulent; tuberculosis)_____
- ☐ Other, please specify: _____

☐ Ear and labyrinth infections
- ☐ Otitis media _____
- ☐ Otitis externa _____
- ☐ Other, please specify: _____

☐ Ear and labyrinth infections
- ☐ Colitis _____
- ☐ Diverticulitis _____
- ☐ Appendicitis _____
- ☐ Abdominal sepsis (including peritonitis) _____
- ☐ Hepatic abscess _____
- ☐ Hepatitis B _____
- ☐ Hepatitis C _____
- ☐ Other, please specify: _____

☐ Musculoskeletal and connective tissue infections
- ☐ Osteomyelitis _____
- ☐ Septic arthritis _____
- ☐ Other, please specify: _____

☐ Nervous system infections
- ☐ Meningitis _____
- ☐ Encephalitis _____
- ☐ Other, please specify: _____

☐ Respiratory tract infections
- ☐ Pneumonia _____
- ☐ Pulmonary TB _____
- ☐ Lung abscess _____
- ☐ Legionnella pneumonia _____
- ☐ Mycoplasma pneumonia _____
- ☐ Other, please specify: _____

☐ Kidney and genito-urinary tract infections
- ☐ Cystitis _____
- ☐ Pyelonephritis _____
- ☐ Urinary tract infection _____
- ☐ Other, please specify: _____

☐ Systemic infections
- ☐ Bacteremia _____
- ☐ Sepsis _____
- ☐ Toxic shock syndrome _____
- ☐ Other, please specify: _____

☐ Wound and skin infections
- ☐ Cellulitis _____
- ☐ Erysipelas _____
- ☐ Necrotizing fasciitis _____
- ☐ Abscess _____
- ☐ Other skin infections, please specify: _____

☐ Opportunistic infections
- ☐ Aspergillus (invasive forms only) _____
- ☐ Blastomycosis pulmonary or extra-pulmonary infections _____
- ☐ Candidiasis systemic _____
- ☐ Coccidioidemycosis secondary/systemic _____
- ☐ Cryptococcal infection- pulmonary and non-pulmonary _____
- ☐ Cytomegalovirus- include systemic site _____
- ☐ Herpes simplex (meningitis or encephalitis) _____
- ☐ Herpes zoster (only systemic or disseminated: involving 2 or more dermatomes) _____
- ☐ Histoplasma infections - chronic disseminated or severe acute _____
- ☐ Mucormycosis (=zygomycosis) including infections due to Rhizopus, Mucor and Absidia of lung, genito-urinary tract, kidney, GIT, skin _____
- ☐ Mycobacterium tuberculosis _____
- ☐ Non-tuberculosis mycobacterium _____
- ☐ Nocardia infection of brain, lungs, kidney, skin _____
- ☐ Paracoccidioides infections of lungs, skin other _____
- ☐ Pneumocystis carinii pneumonia _____
- ☐ Sporotrichosis - disseminated infections _____
- ☐ Toxoplasmosis encephalitis or disseminated _____
- ☐ Other opportunistic infections, please specify: _____

☐ Other, please specify: _____

☐ Parasitic evaluation (ova, etc.) _____

E-mail address:

REPORTER

Name:
Address:
City:
Country:
Email:
Phone: (include country code)

State:
Province:
Postal Code:

Signature_____

Title_____ **Date**_____

DENOSUMAB Core Questionnaire
Infection (continued)

AE Case ID #

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PATIENT/CASE ADMINISTRATIVE INFORMATION (Please indicate dates as DD/MM/YYYY)

Patient Identifier | Patient Initials | Safety Database No.

REPORTS/RELEVANT FINDINGS (Continued) (Please provide dates, baseline information and indicate attachments if available)

DIAGNOSTICS

☐ Cultures done ☐ No ☐ Yes ☐ Unknown
If yes, check which apply:
☐ Blood culture _____
☐ Culture positive ☐ No ☐ Yes ☐Unknown
If yes, which ☐ Bacterial ☐ Fungal ☐ Viral
☐ Pathogen identified: _____
☐ Urine culture _____
☐ Culture positive ☐ No ☐ Yes ☐Unknown
If yes, which ☐ Bacterial ☐ Fungal ☐ Viral
☐ Pathogen identified: _____
☐ Sputum culture _____
☐ Culture positive ☐ No ☐ Yes ☐Unknown
If yes, which ☐ Bacterial ☐ Fungal ☐ Viral
☐ Pathogen identified: _____
☐ Synovial culture _____
☐ Culture positive ☐ No ☐ Yes ☐Unknown
If yes, which ☐ Bacterial ☐ Fungal ☐ Viral
☐ Pathogen identified: _____

☐ Cerebrospinal fluid culture _____
☐ Culture positive ☐ No ☐ Yes ☐Unknown
If yes, which ☐ Bacterial ☐ Fungal ☐ Viral
☐ Pathogen identified:_____
☐ Tissue culture _____
If yes, specify ☐ Brain ☐ Lung ☐ Liver
☐ Kidney ☐ Skin ☐ Bone ☐ Other
☐ Culture positive ☐ No ☐ Yes ☐Unknown
If yes, which ☐ Bacterial ☐ Fungal ☐ Viral
☐ Pathogen identified:_____
☐ Catheter Tip/Line
☐ Culture positive ☐ No ☐ Yes ☐Unknown
If yes, which ☐ Bacterial ☐ Fungal ☐ Viral
☐ Pathogen identified: _____
☐ PPD placement ☐ No ☐ Yes ☐Unknown
If yes, PPD positive ☐ No ☐ Yes ☐Unknown
_____
_____

☐ Parasitic evaluation (ova, etc.) _____
☐ X-ray ☐ No ☐ Yes ☐ Unknown _____
☐ MRI ☐ No ☐ Yes ☐ Unknown _____
☐ CT scan ☐ No ☐ Yes ☐ Unknown _____
_____
☐ Bone scan ☐ No ☐ Yes ☐ Unknown
_____
☐ Other _____
☐ Rapid test _____
☐ Serum titres
_____
☐ Hospital discharge reports _____
_____
☐ Other consult report _____
_____
☐ Provide final diagnosis and treatment, if available (please specify): _____
_____
☐ Outcome and resolution date _____

TREATMENT

☐ ER antibiotics ☐ No ☐ Yes ☐ Unknown
If yes, route
☐ IV ☐ Oral ☐ SC ☐ Both oral and IV
☐ Required hospital admission
☐ No ☐ Yes ☐ Unknown
☐ ICU admission ☐ No ☐ Yes ☐ Unknown
If yes, reason for ICU admission_____

Overall length of hospital stay:
☐ ≤1day ☐ >1day ☐ ≤7days ☐ >7 days
_____
☐ In-hospital antibiotics
☐ No ☐ Yes ☐ Unknown
☐ If yes, route of administration
☐ IV ☐ Oral ☐ Both oral and IV

☐ Other in-hospital treatment
☐ Antivirals ☐ No ☐ Yes ☐ Unknown
If yes, route of administration ☐ IV ☐ Oral
☐ Antfungals ☐ No ☐ Yes ☐ Unknown
If yes, route of administration ☐ IV ☐ Oral
☐ Surgery ☐ No ☐ Yes ☐ Unknown
☐ Hyperbaric oxygen ☐ No ☐ Yes ☐ Unknown

PATIENT HISTORY/RISK FACTORS (Please provide history, dates, severity of reaction and intervention)

Please specify any post operative complications, chronic disease or infection, etc.
☐ Chronic lung disease_____
☐ Hepatitis_____
☐ Chronic kidney disease_____
☐ Liver disease _____
☐ Congenital infections/malformations_____
☐ Osteomyelitis_____
☐ HIV_____
☐ Diabetes mellitus_____
☐ Cancer (specify)_____
☐ Recent wounds/infections _____
☐ Immunosuppression _____
☐ Known exposure to TNF inhibitors_____
☐ Chemotherapy _____
☐ Malnutrition/failure to thrive_____
☐ Exposure to infectious agents_____
☐ Personal contact _____ ☐ Body fluids_____
☐ Share personal items (razor, needles, etc) ___
☐ Potentially contaminated food/liquid_____

Exposure to infectious agents (continued)
☐ Hospital acquired_____
☐ Other_____
☐ Steroid exposure_____
☐ Insect/tick bite_____
☐ Drug or IV drug abuse: Type_____
Amount_____
Frequency_____
☐ Alcohol/tobacco use: Type_____
Amount_____
Frequency_____
☐ Indwelling catheters_____
_____
_____
☐ Recent skin injury
_____
_____
☐ Recent travel (specify)
_____
_____

☐ Exposure to animals/zoonotic diseases (exposure to infected animal)_____
☐ Unprotected sex_____
☐ Immobility_____
☐ Indwelling catheters_____
☐ Nursing home resident_____
☐ Occupational exposure_____
☐ Ostomy_____
☐ Post influenza_____
☐ Surgery< 30 days_____
☐ TB exposure_____
☐ Other history/risk factors_____

E-mail address:

REPORTER

Name:
Address: State:
City: Province:
Country: Postal Code:
Email:
Phone: (include country code)
Signature_____
Title_____**Date**_____

DENOSUMAB Core Questionnaire
Malignancy

AE Case ID #

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Office Patient Identifier _____Patient Initials _____

Questionnaire for Malignancy Adverse Events

Date of event onset (DD/MM/YYYY): _____/_____/_____

Is this a new primary malignancy? Yes ☐ No ☐ Unknown ☐

If no, is this a recurrence of a previous cancer? Yes ☐ No ☐ Unknown ☐

Does patient have history of other malignancy? Yes ☐ No ☐ Unknown ☐

If yes, date of prior cancer (DD/MM/YYYY): _____/_____/_____

Tumor stage, if known: _____

Primary site of malignancy: _____

Tumor Stage:

Tumor Size (Check which one applies):

TX ☐ TO ☐ Tis ☐ T1 ☐ T2 ☐ T3 ☐ T4 ☐

Tumor Grade (Check which one applies):

GX ☐ G1 ☐ G2 ☐ G3 ☐

Localized (no regional involvement/no distant metastasis)? Yes ☐ No ☐

(If yes, skip next 2 questions)

Lymph Node Involvement (Check which one applies):

NX ☐ N1 ☐ N2 ☐ N3 ☐

Metastases (Check which one applies):

MX ☐ M0 ☐ M1 ☐

DENOSUMAB Core Questionnaire
Malignancy

AE Case ID #

TREATMENT:

Hospitalized? Yes ☐ No ☐ Unknown ☐

ICU admission? Yes ☐ No ☐ Unknown ☐

Overall length of hospital stay: ≤ 1 day ☐ > 1 day or ≤ 7 days ☐ > 7 days ☐

Surgical treatment? Yes ☐ No ☐ Unknown ☐

Chemotherapy (includes biologics)? Yes ☐ No ☐ Unknown ☐

Hormonal treatment? Yes ☐ No ☐ Unknown ☐

Radiation treatment? Yes ☐ No ☐ Unknown ☐

Bone marrow transplant? Yes ☐ No ☐ Unknown ☐

If yes, autologous ☐ heterologous ☐

Was the malignancy treated with curative intention? Yes ☐ No ☐ Unknown ☐

RISK FACTORS (Check all that apply):

Smoking ☐

Prior Malignancy ☐

Positive Family History (Check all that apply):

Same cancer ☐

Different cancer ☐

Prior therapeutic radiation exposure ☐

Environmental exposure ☐

Specify: _____

DENOSUMAB Core Questionnaire
Osteonecrosis of the Jaw

AE Case ID #

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PATIENT / CASE ADMINISTRATIVE INFORMATION (Please indicate all dates as DD/MM/YYYY)

Patient Identifier

Patient Initials

Date of Event Onset

Date of This Report

Gender: ☐Male ☐Female Weight:_____lb _____Kg

Age at time of event:_____

Event Reported Term

Study No.

☐Clinical Trial
☐Post-Marketing

Safety Database No.

DENOSUMAB ADMINISTRATION / INFORMATION (Please indicate dates as DD/MM/YYYY)

Denosumab Indication

☐ Postmenopausal osteoporosis
☐ Bone loss from hormone ablation therapy
Please specify diagnosis _____
☐ Advanced cancer with bone metastasis
Please specify cancer_____
☐ Other
Please Specify_____
☐ Don't know

Denosumab Dose

☐ 60 mg SC every 6 months ☐ 120 mg SC every 4 weeks
☐ Other Please specify_____
☐ Don't know

Denosumab Exposure

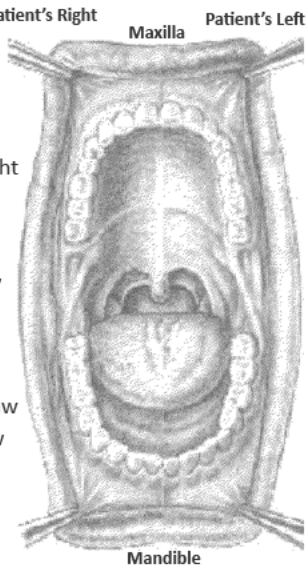
Denosumab first administered (date) _____
Last Denosumab dose before event (date) _____
☐ Doses of denosumab were skipped ☐No☐Yes☐Unknown
If yes, please specify _____
☐ Doses of denosumab given after event began ☐No ☐Yes☐ Unknown
If yes, date of first dose following start of event _____

EVIDENCE OF EXPOSED BONE (Please indicate dates as DD/MM/YYYY)

Visible evidence of exposed bone, or bone that can be probed through an intraoral or extraoral fistula(e) in the maxillofacial region:
☐ No ☐ Yes ☐ Unknown; Please describe _____

Date exposed bone was first visualized/probed:_____
Exposed bone or probed bone that has persisted for more than eight weeks: ☐ No ☐ Yes ☐ Unknown
Prior history of radiation therapy to jaw:
☐ No ☐ Yes ☐ Unknown
Prior history of metastatic disease to jaw:
☐ No ☐ Yes ☐ Unknown
Describe: _____

Please indicate the location of involved area(s) on the diagram at right (mark site(s) clearly with "X").



Please describe location(s):
☐ Right maxilla, teeth and lateral jaw
☐ Left maxilla, teeth and lateral jaw
☐ Right maxilla, medial jaw
☐ Left maxilla, medial jaw
☐ Right mandible teeth and lateral jaw
☐ Left mandible teeth and lateral jaw
☐ Right mandible, medial jaw
☐ Left mandible, medial jaw
☐ Maxilla hard palate
☐ Other (specify) _____

Oral Findings

Evidence of infection: ☐ No ☐ Yes ☐ Unknown
Please describe _____

Exposed bone at the site of extraction: ☐ No ☐ Yes ☐ Unknown

Complete coverage of involved area(s) by mucosa:
☐No ☐Yes ☐Unknown
If yes, date of complete mucosal coverage _____

CLINICAL SYMPTOMS (Please indicate dates as DD/MM/YYYY)

Date of first clinical signs/symptoms in the mouth (eg. Infection, pain, inflammation): _____
Please describe the clinical signs/symptoms/location:

REPORTER

Name:
Address:
City: State/
Country: Province:
Email: Postal Code:
Phone: (include country code)
Signature _____
Title_____**Date**_____

DENOSUMAB Core Questionnaire
Osteonecrosis of the Jaw (Continued)

AE Case ID #

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PATIENT / CASE ADMINISTRATIVE INFORMATION (Please indicate all dates as DD/MM/YYYY)

Patient Identifier | Patient Initials | Safety Database No.

CONSULTATIONS (Please indicate all dates as DD/MM/YYYY)

Dental / oral surgery / stomatology consultations ☐ No ☐ Yes ☐ Unknown If yes, please give date examination _____

Please provide any consult reports, radiographs, pictures if available _____

TREATMENT INFORMATION (Please indicate what treatments were administrated and indicate dates as DD/MM/YYYY)

Antibiotics ☐ No ☐ Yes ☐ Unknown If yes, agent(s)/route/dose_____Start date_____Stop date_____

Please describe outcomes of treatment _____

Oral rinses ☐ No ☐ Yes ☐ Unknown If yes, agent(s)/dose_____

Please describe outcomes of treatment _____

Oral surgery ☐ No ☐ Yes ☐ Unknown If yes, type of surgery_____

Start date_____Stop date_____

Please describe outcomes of treatment_____

Hospitalizations ☐ No ☐ Yes ☐ Unknown If yes, reason for hospitalization_____

Hospitalization begin date_____ Hospitalization end date_____

Please describe outcomes of treatment _____

DENTAL HISTORY (Please indicate all dates as DD/MM/YYYY)

History of poor oral hygiene ☐ No ☐ Yes ☐ Unknown _____

Dental extraction recently ☐ No ☐ Yes ☐ Unknown If yes, Date of procedure _____

Dental surgery recently ☐ No ☐ Yes ☐ Unknown If yes, Date of procedure _____

Periodontal disease including gingival bleeding, calculus, etc. ☐ No ☐ Yes ☐ Unknown Start date_____ Stop date _____

Draining fistula in affected area ☐ No ☐ Yes ☐ Unknown Start date_____ Stop date _____

Dental abscess in affected area ☐ No ☐ Yes ☐ Unknown Start date_____ Stop date _____

Osteomyelitis in affected area ☐ No ☐ Yes ☐ Unknown Start date_____ Stop date _____

Root-canal treatment near affected area ☐ No ☐ Yes ☐ Unknown If yes, date of treatment _____

Dental treatment, surgery or tooth extraction to the involved area within the last 4-6 months PRIOR to the onset of the oral lesion
☐ No ☐ Yes ☐ Unknown

History of dentures / dental appliance / implant ☐ No ☐ Yes ☐ Unknown If yes, please specify ☐ Upper ☐ Lower

Area of lesion at or near a contact point ☐ No ☐ Yes ☐ Unknown

MEDICATIONS (Please indicate all dates as DD/MM/YYYY)

PO bisphosphonate ☐ No ☐ Yes ☐ Unknown If yes, agent(s)/dose _____

Start date_____ Stop date _____

IV bisphosphonate ☐ No ☐ Yes ☐ Unknown If yes, agent(s)/dose _____

Start date_____ Stop date _____

Glucocorticoid use within the past 12 months ☐ No ☐ Yes ☐ Unknown If yes, agent(s)/dose _____

Start date_____ Stop date _____

Immunosuppressant use within the past 12 months ☐ No ☐ Yes ☐ Unknown If yes, agent(s)/dose _____

Start date_____ Stop date _____

Chemotherapy within the past 12 months ☐ No ☐ Yes ☐ Unknown If yes, agent(s)/dose _____

Start date_____ Stop date _____

Anti-angiogenic agents (e.g. bevacizumab) within the past 12 months ☐ No ☐ Yes ☐ Unknown If yes, agent(s)/dose _____

Start date_____ Stop date _____

OTHER HISTORY (Please indicate all dates as DD/MM/YYYY)

Current smoker ☐ No ☐ Yes ☐ Unknown

If yes, estimated number of pack-years _____

If past smoker, stop date _____

Alcohol consumption ☐ No ☐ Yes ☐ Unknown

If yes, estimated of drinks per week _____

Diabetes ☐ No ☐ Yes ☐ Unknown If yes, ☐ Type I ☐ Type II

PATIENT REMINDER CARD STATUS (for EU patients)

Received a patient reminder card prior to the ONJ event:
☐ No ☐ Yes ☐ Unknown

_____

_____

E-mail Address:

DENOSUMAB Core Questionnaire

POSTMARKETING REPORTS OF POTENTIAL ATYPICAL FRACTURE

(low energy, subtrochanteric/femoral shaft fractures)

AE Case ID #

This form is subject to applicable laws governing the protection of personal information. The information provided on this form is collected for pharmacovigilance purposes, may be transferred, and processed outside of the country in which it is collected. mAbxience does not wish to receive information through which a patient can be identified therefore do not provide any information other than the specific information required by this form. This prohibition includes, for example, name, address, telephone number and government issued identifier.

PATIENT/CASE ADMINISTRATIVE INFORMATION (Please indicate dates as DD/MM/YYYY)

Patient Identifier	Patient Initials	Date of Event Onset	Date of this report

Gender: ☐ Male ☐ Female Weight:_____lb _____Kg

Age at the time of event: _____

Study Number (If applicable).

Event

DENOSUMAB ADMINISTRATION/INFORMATION (Please indicate dates as DD/MM/YYYY)

Denosumab indication:

☐ Postmenopausal osteoporosis

☐ Bone loss from hormone ablation therapy

Please specify diagnosis_____

_____

☐ Advanced cancer with bone metastasis

Please specify cancer_____

☐ Other (please specify) _____

_____

☐ Don't know_____

Denosumab Dose:

☐ 60 mg SC every 6 months ☐ 120 mg SC every 4 weeks

☐ Other (please specify) _____ ☐ Don't know

Denosumab Exposure:

Denosumab first administered (date)_____

Last denosumab dose before event (date)_____

Doses of denosumab were skipped ☐ Yes ☐ No ☐ Unknown

If yes, please specify_____

Doses of denosumab given after event began ☐ Yes ☐ No ☐ Unknown

If yes, date of first dose following start of event _____

DIAGNOSIS (Check all that apply)

Location of fracture:

☐ Femur neck
☐ Femur distal
☐ Femur midshaft
☐ Femur intertrochanter
☐ Femur subtrochanter
☐ Other location (specified)_____

Diagnostic imaging used to confirm fracture

☐ X-ray ☐ CT scan ☐ MRI

Date of imaging at time of femur fracture (DD/MM/YYY): _____

☐ **Please attach a copy of applicable radiology report (s)**

Was this a pathological fracture associated with bone tumor or miscellaneous bone diseases (e.g. Paget's disease, fibrous dysplasia)

☐ Yes ☐ No ☐ Unknown

Type of fracture:

☐ Transverse
☐ Oblique
☐ Spiral
☐ Not reported

Fracture radiology report includes:

Simple transverse or oblique (30°) fracture with beaking of the cortex:

☐ Yes ☐ No ☐ Not reported

Diffuse cortical thickening of the proximal femoral shaft:

☐ Yes ☐ No ☐ Not reported

Type of trauma reporter at time of fracture:

☐ No trauma
☐ Fall from standing height or less
☐ Fall on stair, steps or curbs
☐ Fall from the height of stool, chair, first rung on a ladder or equivalent (about 20 inches)
☐ Minimal trauma other than fall

☐ Fall from higher than the height of a stool, chair, first rung on ladder or equivalent (> 20 inches)
☐ Severe trauma other than a fall (e.g., car accident)
☐ Unknown type of trauma

Early symptom of pain over fracture site

☐ Pain at the site at rest
☐ Pain at the site with weight bearing
☐ None

Fracture healed (union) within 6 months ☐ Yes ☐ No ☐ Unknown

If yes:

☐ Date of fracture union (DD/MM/YYY)_____

☐Patient able to walk without assistance ☐ Yes ☐ No ☐ Unknown

☐ Fracture union confirmed through imagine ☐ Yes ☐ No ☐ Unknown

If yes, check all diagnostic imaging that applies: ☐ X-ray ☐ CT scan ☐ MRI

DENOSUMAB Core Questionnaire

POSTMARKETING REPORTS OF POTENTIAL ATYPICAL FRACTURE

(low energy, subtrochanteric/femoral shaft fractures)

AE Case ID #

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PATIENT/CASE ADMINISTRATIVE INFORMATION (Please indicate all dates as DD/MM/YYYY)

Patient Identifier

Patient Initials

Date of this report

TREATMENT (Please provide dates and indicate attachments if available)

Methods to reduce and set fracture:

☐ Non-surgical reduction_____

☐ Casting_____

☐ Surgery_____ _____

☐ Revision surgery (2nd surgery_____

☐ Other_____

☐ Unknown_____

MEDICAL HISTORY/RISK FACTORS (Check all that apply, provide dates and attach relevant reports)

General

☐ History or current corticosteroid use

☐ Affected hip with prior surgical pinning

☐ Affected hip with prior hip replacement

Cancer:

Evidence of any metastases ☐ Yes ☐ No ☐ Unknown

If yes, did metastasis involve bone? ☐ Yes ☐ No ☐ Unknown

Metastasis in femur where fracture occurred? ☐ Yes ☐ No ☐ Unknown

Prior osteoporosis therapy:

☐ Estrogen

☐ Selective estrogen receptor modulator (SERM)

☐ Bisphosphonate (please indicate)

☐ Intravenous ☐ Oral

If yes, how long has therapy been received? (months, years)

☐ Parathyroid hormone

Past medical and surgical history

_____

_____

_____

Medication history (include dose, frequency, and dates of treatment):

_____

_____

_____

Copies of records/consults/radiology report attached ☐ Yes ☐ No ☐

_____

_____

_____

REPORTER

Name:

Address:

City: State:

Country: Province:

Email: Postal Code:

Phone (include country code):

Signature_____

Title_____ **Date**_____

E-mail address:

Annex 6 - Details of proposed additional risk minimisation measures

ZADENVI has additional risk minimisation measures for its safe and effective use (additional risk minimisation measures).

Key elements for the ZADENVI educational material (Patient Reminder Card)

In alignment with the EMA requirements for Prolia®, key elements to be included in the patient educational material are as follows:

Patient reminder card:

Patient Reminder Cards for osteonecrosis of the jaw (ONJ) will be distributed to prescribers of ZADENVI with the background information on the purpose of the patient reminder card and instructions to provide it to patients.

The patient reminder card will remind patient about important safety information that the need to be aware of before and during treatment with denosumab (ZADENVI) injections for osteoporosis and bone loss, including:

- The risk of osteonecrosis of the jaw during treatment with ZADENVI;
- The need to highlight any problems with their mouth or teeth to their doctors/nurses before starting treatment.
- The need to ensure good oral hygiene during treatment;
- The need to inform their dentist of treatment with ZADENVI and to contact their doctor and dentist if problems with the mouth or teeth occur during treatment.

The patient reminder card will be distributed by mail and prescribers will be provided with contact details to request additional copies of the card. Some national plans will include making the patient reminder card available on a website and this approach may be extended in the future.

In addition, the focused questionnaire for postmarketing reports of ONJ presented in *Annex 4*.