EU RISK MANAGEMENT PLAN

Ponlimsi (Denosumab)

(60 mg/mL solution for injection)

RMP version to be assessed as part of this application	
RMP version number	1.1
Data lock point for this RMP	11 July 2024
Date of final sign off	10 March 2025
Rationale for submitting an updated RMP	Not applicable.
Summary of Significant Changes in This RMP	Not applicable.

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

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AFF	Atypical Femoral Fracture
AIDS	Acquired Immunodeficiency Syndrome
ARMM	Additional Risk Minimisation Measure
ATC	Anatomical Therapeutic Chemical
AUC	Area Under The Curve
BMD	Bone Mineral Density
CrCL	Creatinine Clearance
CTD	Common Technical Document
e.g.	Example Given
DLP	Data Lock Point
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
HIV	Human Immunodeficiency Virus
IgE	Immunoglobulin E
IgG	Immunoglobulin G
INN	International Non-Proprietary Name
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
ONJ	Osteonecrosis of the Jaw
OPG	Osteoprotegerin
PL	Package Leaflet
PSUR	Periodic Safety Update Report
Q6M	Every 6 Months
QPPV	Qualified Person for Pharmacovigilance
RANKL	Receptor Activator of Nuclear Factor-κB Ligand
RMP	Risk Management Plan
SmPC	Summary Of Product Characteristics
WHO	World Health Organisation

Part I: Product(s) Overview

Table 1: Product(s) Overview

Active substance(s) (INN or common name)	**Denosumab**
Pharmacotherapeutic group(s) (ATC Code)	Drugs for treatment of bone diseases; other drugs affecting bone structure and mineralization (M05BX04)
Marketing Authorisation Holder/Applicant	TEVA GmbH Graf-Arco-Strasse 3 Donautal, Ulm Baden-Wuerttemberg 89079, Germany
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Ponlimsi
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class**: Denosumab is a fully human monoclonal antibody of the immunoglobulin G (IgG) 2 subclass.
	Summary of mode of action: Binds to and neutralizes the activity of the human RANK ligand (RANKL). In blocking RANKL, denosumab reduces osteoclast-mediated bone resorption.
	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	Please refer to 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 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 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 (if applicable): Not applicable.
Dosage in the EEA	**Current**: The recommended dose is 60 mg denosumab administered as a single subcutaneous injection once every 6 months into the thigh, abdomen, or upper arm. Patients must be adequately supplemented with calcium and vitamin D.
	Proposed (if applicable): Not applicable.
Pharmaceutical form(s) and strengths	**Current**: 60 mg/mL solution for injection in pre-filled syringe (intended for subcutaneous use). Each pre-filled syringe contains 60 mg of denosumab in 1 mL of solution (60 mg/mL).
	Proposed (if applicable): Not applicable.
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety Specification

Part II: Module SI - Epidemiology of the Indication(s) and Target Population(s)

Since Teva's Denosumab is a biosimilar (application under Article 10(4) of Directive 2001/83/EC) to Prolia® (Amgen Europe B.V.), in line with Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (Rev 2) (EMA/838713/2011 Rev 2), Part II: Module SI is not applicable.

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

Teva's Denosumab (TVB-009) was developed as a biosimilar candidate to the reference product denosumab approved worldwide under the trade name PROLIA® (Amgen).

In vitro assays

Characterization of TVB-009 structural and functional parameters, and additional biosimilarity assessment to evaluate the similarity between TVB-009 and US and EU PROLIA® was performed. The functional *in vitro* assay panel covered activities associated with the mechanism of action and pharmacodynamics, including testing RANKL ligand binding and affinity, osteoclast cell line differentiation and cell signalling. Binding to FcRn and the potential for effector function (Fcγ receptor and C1q binding assays, and complement dependent cytotoxicity and antibody-dependent cell cytotoxicity cell assays) were also evaluated.

Results of the testing indicate TVB-009 has the expected activity to bind RANKL and inhibit RANKL-induced osteoclast differentiation activity with low potential for effector functional activity. For Complement Dependent Cytotoxicity (CDC) activity, although the biosimilar showed higher CDC activity compared to the originator, the overall CDC activity levels for both drugs remained low. Overall TVB-009 had expected *in vitro* activity, similar to US licensed PROLIA® and EU-approved comparator PROLIA®.

In vivo non-clinical study (single-dose)

The safety, pharmacokinetics (PK), pharmacodynamics (PD) and immunogenicity of TVB-009 were investigated in a nonclinical *in vivo* single-dose study in cynomolgus monkeys designed to support the safety and demonstration of TVB-009 similarity to the reference product PROLIA® (US). In this single-dose comparative subcutaneous study (DS-2018-00649), cynomolgus monkeys were dosed once with 1 mg/kg TVB-009 or PROLIA® (US) and followed for a period of 43 days.

TVB-009 was well tolerated and no meaningful treatment related effects were noted in TVB-009 or PROLIA® (US) treated animals in clinical observations, local tolerance, changes in body weights, food consumption, clinical pathology, urinalysis, organ weights, gross pathology, and histopathology of selected organs.

Following 1 mg/kg single subcutaneous administration, similar absorption profile and exposure parameters were observed for TVB-009 and PROLIA® (US). Faster elimination observed in

TVB-009 versus PROLIA® (US) treated animals was likely associated with earlier anti-drug antibodies (ADA) formation in TVB-009 treated animals.

Bone turnover biochemical markers, alkaline phosphatase (ALP) and serum calcium, showed the expected effect following the administration of 1 mg/kg TVB-009 and PROLIA®. ALP and serum calcium levels, in males and females of both treatment groups decreased in a comparable manner reaching lowest levels on Day 15, and then returning to near baseline levels by Day 44.

In conclusion, the nonclinical study demonstrated comparability between TVB-009 and PROLIA® (US) with respect to safety, exposure and pharmacodynamic endpoints.

Repeat-dose toxicity, genotoxicity, carcinogenicity, reproduction and developmental studies, as well as tissue distribution, plasma protein binding, metabolism, excretion, and nonclinical drug-drug interaction studies were not performed in line with the relevant guidance for preclinical evaluation of biosimilar products.

Key safety findings from innovator's nonclinical studies and relevance to human usage

The findings from the innovator's (Prolia®, Amgen Europe B.V.) nonclinical studies are summarized below and are considered relevant also for Teva's biosimilar denosumab.

Table 2: Key safety findings from nonclinical studies and relevance to human usage (based on Prolia® SmPC and the Canadian Product Monograph for Prolia®)

Study type	Important Nonclinical Safety Findings	Relevance to Human Usage
Repeated dose toxicity	Repeated dose toxicity studies were performed in cynomolgus monkeys. Consistent with the pharmacological action of denosumab, there were rapid and marked decreases in circulating markers of bone turnover at all doses. Correlating with these changes, there was increased bone mineral density observed in males and females. In addition, there was enlargement of the growth plates, decreased osteoblasts and osteoclasts, and decreased chondroclasis observed. These changes were recovered or recovering following three treatment-free months. There were no treatment related changes in opthalmoscopy, cardiovascular physiology, sperm motility and morphology, circulating immunoglobulins and lymphocyte subsets, or organ weights (Prolia® Canadian Product Monograph).	Calcium levels were transiently decreased and parathyroid hormone levels transiently increased in ovariectomised monkeys treated with denosumab (Prolia® SmPC, 5.3). Patients must be adequately supplemented with calcium and vitamin D during denosumab therapy (Prolia® SmPC, 4.2 and 4.4). Hypocalcaemia is a contraindication for denosumab (Prolia® SmPC, 4.3). Special warnings and precautions for use (Prolia® SmPC, 4.4): Adequate intake of calcium and vitamin D is important in all patients. Hypocalcaemia must be corrected by adequate intake of calcium and vitamin D before initiating therapy. Clinical monitoring of calcium levels is recommended before each dose and, in patients predisposed to hypocalcaemia within two weeks after the initial dose. Patients with severe renal impairment (creatinine clearance < 30 mL/min) or receiving dialysis are at greater risk of developing hypocalcaemia. Adequate intake of calcium, vitamin D and regular monitoring of calcium is especially important in these patients.

Study type	Important Nonclinical Safety Findings	Relevance to Human Usage
Reproductive toxicity	At area under the curve (AUC) exposures up to 100-fold higher than the human exposure (Q6M), denosumab showed no evidence of impaired fertility in cynomolgus monkeys (Prolia® Canadian Product Monograph). In a study of cynomolgus monkeys dosed with denosumab during the period equivalent to the first trimester at AUC exposures up to 99-fold higher than the human dose (Q6M), there was no evidence of maternal or foetal harm. In this study, foetal lymph nodes were not examined (Prolia® SmPC, 5.3). In cynomolgus monkeys dosed with denosumab throughout pregnancy, effects including stillbirths and increased postnatal mortality; abnormal bone growth, reduced haematopoiesis, and tooth malalignment; absence of peripheral lymph nodes; and decreased neonatal growth were noted at AUC exposures up to 119-fold higher than the human exposure (60 mg Q6M). There was no evidence of maternal harm prior to labor; adverse maternal effects occurred infrequently during labor. Maternal mammary gland development was normal (Prolia® SmPC, 5.3). In genetically engineered mice in which RANKL has been turned off by gene removal (a "knockout mouse"), studies suggest absence of RANKL during pregnancy may interfere with maturation of the mammary gland leading to impaired lactation post-partum (Prolia® SmPC, 4.6).	Cynomolgus monkeys exposed to denosumab in utero phenotypically resembled human infants with osteoclast-poor osteopetrosis due to inactivating mutations of RANK or RANKL. Therefore, denosumab is not recommended for use in pregnant women. Women should be advised not to become pregnant during and for at least 5 months after treatment with denosumab (Prolia® SmPC, 4.6). It is not known if denosumab is excreted in human milk. Because denosumab has the potential to cause adverse reactions in nursing infants, a decision should be made on whether to discontinue nursing or discontinue the drug (Prolia® SmPC, 4.6). Use in pregnant and lactating women is not considered a safety concern in this RMP. These populations are not included in the intended indications. In addition, risk minimization via product labelling to avoid pregnancy and breastfeeding is in place.

Study type	Important Nonclinical Safety Findings	Relevance to Human Usage
Developmental toxicity	In neonatal cynomolgus monkeys exposed in utero to denosumab, there was increased postnatal mortality; abnormal bone growth resulting in reduced bone strength, reduced haematopoiesis, and tooth malalignment; absence of peripheral lymph nodes; and decreased neonatal growth. Following a 6 month period after birth, bone related changes showed recovery and there was no effect on tooth eruption; minimal to moderate mineralisation in multiple tissues was seen in one animal (Prolia® SmPC, 5.3). Adolescent primates dosed with denosumab at 27 and 150 times the clinical exposure had abnormal growth plates (Prolia® SmPC, 5.3).	Treatment with denosumab may inhibit eruption of dentition in paediatric patients and may impair bone growth in paediatric patients with open growth plates (Prolia® SmPC 5.3, Prolia® Canadian Product Monograph). Use in paediatric patients is not considered a safety concern in this RMP. Denosumab is not approved for use in paediatric patients. Risk minimization is in place via product labelling with respect to use in paediatric patients.

Part II: Module SIII - Clinical Trial Exposure

Teva's Denosumab (TVB 009) has been developed as a biosimilar candidate to PROLIA® and XGEVA® (Amgen) with the active substance denosumab. TVB-009 has been developed in 2 forms (TVB-009P and TVB-009X) as a biosimilar candidate to denosumab (PROLIA® and XGEVA, respectively). TVB-009P was developed as a single-use prefilled syringe (PROLIA® configuration) and TVB-009X as a single-use vial (XGEVA configuration).

This RMP is dedicated to the denosumab 60 mg/mL solution for injection in a pre-filled syringe (TVB-009P), which was developed as a biosimilar to the reference product Prolia® with an adequate biosimilar clinical development program.

As a part of the clinical development program, two studies have been conducted and completed:

- Study TVB009-BE-10157 (a Phase 1 PK/PD study in healthy participants; referred to as Study 10157): a single-center, double-blind, randomized, parallel group, single dose study to investigate the PK/PD similarity of a 60 mg subcutaneous dose of TVB-009P (denosumab 60 mg/mL solution for injection in a single-use pre-filled syringe) with PROLIA® sourced from the EU and US, in 345 healthy adult (over 28 years of age) male and female participants. The study consisted of 4 weeks of screening and 36 weeks of treatment/observation period.
- Study TVB009-IMB-30085 (a Phase 3 comparative efficacy and safety study in patients with postmenopausal osteoporosis): a randomized, double blind, multinational, multicenter study with an objective to demonstrate similar efficacy, safety and immunogenicity of TVB 009P compared to PROLIA® US in 332 patients with postmenopausal osteoporosis. At baseline, participants received the first 2 doses of 60 mg TVB 009P or PROLIA® US at day 1 and week 26 (“main treatment period”). At week 52 (26 weeks after the second dose; “transition period”), participants in the PROLIA® US arm either continued with a third dose of PROLIA® US or transitioned to TVB 009P to assess primarily immunogenicity and safety after a single transition from PROLIA® to TVB 009P. Total time of follow-up was 78 weeks.

In Study 10157, a total of 345 healthy adult (over 28 years of age to ensure skeletal maturation) male and female participants were treated with study medication, of which 115 participants received TVB-009P (60 mg as a single subcutaneous injection).

Table 3: Study 10157: Exposure in healthy participants by gender, race group and ethnicity

	TVB-009P (60 mg) N = 115 n (%)	**Prolia US (60 mg) N = 115 n (%)**	**Prolia EU (60 mg) N = 115 n (%)**
Gender			
Male	50 (43)	62 (54)	62 (54)
Female	65 (57)	53 (46)	53 (46)
Race group			
White	103 (90)	97 (84)	107 (93)

Black or African American	12 (10)	18 (16)	8 (7)
Ethnicity			
Hispanic or Latino	115 (100)	115 (100)	114 (>99)
Not Hispanic or Latino	0	0	1 (<1)

Source data: Listing 16.2.4.1 (data extract: 15 October 2020).

In study 30085 in patients with postmenopausal osteoporosis, a total of 332 participants were randomised, 331 patients received at least one dose of study medication: during the main treatment period (up to two doses), 166 participants were treated with TVB 009P (denosumab 60 mg/mL solution for injection in a single-use pre-filled syringe) and 165 participants with PROLIA® US. In the transition period (week 52 to week 78), of the patients treated with TVB 009P, 148 patients received a third dose. Of the participants treated with PROLIA® US, 71 participants were treated with one further dose of TVB 009P and 72 participants continued PROLIA® US, in the transitions period (week 52 to week 78).

Table 4: Study 30085: Exposure in patients with postmenopausal osteoporosis (in the main treatment period; Safety Analysis Set)

	TVB 009P (60 mg) N = 166		**Prolia US (60 mg) N = 165**	
Number of doses	**Patients n (%)**	**Patient-time (months)**	**Patients n (%)**	**Patient-time (months)**
1 dose	8 (4.8%)	45.8	12 (7.3%)	74.6
2 doses	158 (95.2%)	1894.9	153 (92.7%)	1848.8
Total	166 (100.0%)	1940.6	165 (100.0%)	1923.5

Source: Table Ad-hoc 1 (data extract: 07 September 2023). Patient-time is the sum of each patient's treatment exposure in months, derived as (date of last visit in the main treatment period if no transition period or date of first dose in transition period – date of first dose +1)/30.25.

Table 5: Study 30085: Exposure in patients with postmenopausal osteoporosis (in the transition period; Transition Safety Analysis Set)

TVB 009P/TVB 009P (60 mg/60 mg) N = 148		**Prolia US/Prolia US (60 mg/60 mg) N = 72**		**Prolia US/TVB 009P (60 mg/60 mg) N = 71**	
Patients n (%)	**Patient-time (months)**	**Patients n (%)**	**Patient-time (months)**	**Patients n (%)**	**Patient-time (months)**
148 (100.0%)	864.4	72 (100.0%)	423	71 (100.0%)	419.8

Source: Table Ad-hoc 2 (data extract: 07 September 2023). Patient-time is the sum of each patient's treatment exposure in months, derived as (date of last visit – date of first dose in the transition period +1)/30.25.

Table 6: Study 30085: Exposure in patients with postmenopausal osteoporosis by age group (in the main treatment period; Safety Analysis Set)

	TVB 009P (60 mg) N = 166		Prolia US (60 mg) N = 165	
Age group / number of doses	**Patients n (%)**	**Patient-time (months)**	**Patients n (%)**	**Patient-time (months)**
<65 years				
1 dose	3 (1.8%)	12.3	3 (1.8%)	18.4
2 doses	44 (26.5%)	527.9	53 (32.1%)	638
Total	47 (28.3%)	540.2	56 (33.9%)	656.4
≥65 years				
1 dose	5 (3.0%)	33.4	9 (5.5%)	56.3
2 doses	114 (68.7%)	1367	100 (60.6%)	1210.8
Total	119 (71.7%)	1400.4	109 (66.1%)	1267.1

Source: Table Ad-hoc 3 (data extract: 07 September 2023). Patient-time is the sum of each patient's treatment exposure in months, derived as (date of last visit in the main treatment period if no transition period or date of first dose in transition period – date of first dose +1)/30.25.

Table 7: Study 30085: Exposure in patients with postmenopausal osteoporosis by age group (in the transition period; Transition Safety Analysis Set)

	TVB 009P/TVB 009P (60 mg/60 mg) N = 148		Prolia US/Prolia US (60 mg/60 mg) N = 72		Prolia US/TVB 009P (60 mg/60 mg) N = 71	
Age group	**Patients n (%)**	**Patient-time (months)**	**Patients n (%)**	**Patient-time (months)**	**Patients n (%)**	**Patient-time (months)**
<65 years	37 (25.0%)	218	26 (36.1%)	152.5	24 (33.8%)	140.2
≥65 years	111 (75.0%)	646.4	46 (63.9%)	270.6	47 (66.2%)	279.6

Source: Table Ad-hoc 4 (data extract: 07 September 2023). Patient-time is the sum of each patient's treatment exposure in months, derived as (date of last visit – date of first dose in the transition period +1)/30.25.

Table 8: Study 30085: Exposure in patients with postmenopausal osteoporosis by race group/ethnicity (in the main treatment period; Safety Analysis Set)

	TVB 009P (60 mg) N = 166		Prolia US (60 mg) N = 165	
	Patients n (%)	**Patient-time (months)**	**Patients n (%)**	**Patient-time (months)**
Race group /dose				

White				
1 dose	8 (4.8%)	45.8	12 (7.3%)	74.6
2 doses	157 (94.6%)	1882.4	151 (91.5%)	1824.6
Total	165 (99.4%)	1928.1	163 (98.8%)	1899.2
Black or African American				
1 dose	0	0	0	0
2 doses	1 (0.6%)	12.5	1 (0.6%)	11.8
Total	1 (0.6%)	12.5	1 (0.6%)	11.8
Not Reported or Unknown				
1 dose	0	0	0	0
2 doses	0	0	1 (0.6%)	12.4
Total	0	0	1 (0.6%)	12.4
Ethnicity /dose				
Hispanic or Latino				
1 dose	2 (1.2%)	13.1	3 (1.8%)	17.3
2 doses	21 (12.7%)	253.5	15 (9.1%)	178.8
Total	23 (13.9%)	266.6	18 (10.9%)	196.1
Not Hispanic or Latino				
1 dose	6 (3.6%)	32.6	9 (5.5%)	57.4
2 doses	137 (82.5%)	1641.4	138 (83.6%)	1670
Total	143 (86.1%)	1674	147 (89.1%)	1727.3

Source: Table Ad-hoc 5 (data extract: 07 September 2023). Patient-time is the sum of each patient's treatment exposure in months, derived as (date of last visit in the main treatment period if no transition period or date of first dose in transition period – date of first dose +1)/30.25.

Table 9: Study 30085: Exposure in patients with postmenopausal osteoporosis by race group/ethnicity (in the transition period; Transition Safety Analysis Set)

	TVB 009P/TVB 009P (60 mg/60 mg) N = 148		**Prolia US/Prolia US (60 mg/60 mg) N = 72**		**Prolia US/TVB 009P (60 mg/60 mg) N = 71**	
	Patients n (%)	**Patient-time (months)**	**Patients n (%)**	**Patient-time (months)**	**Patients n (%)**	**Patient-time (months)**
Race group						
White	147 (99.3%)	857.8	71 (98.6%)	417.7	70 (98.6%)	414

Black or African American	1 (0.7%)	6.6	1 (1.4%)	5.4	0	0
Not Reported or Unknown	0	0	0	0	1 (1.4%)	5.8
Ethnicity						
Hispanic or Latino	21 (14.2%)	121.8	10 (13.9%)	59.2	4 (5.6%)	18.6
Not Hispanic or Latino	127 (85.8%)	742.6	62 (86.1%)	363.9	67 (94.4%)	401.2

Source: Table Ad-hoc 6 (data extract: 07 September 2023). Patient-time is the sum of each patient's treatment exposure in months, derived as (date of last visit in the main treatment period if no transition period or date of first dose in transition period – date of first dose +1)/30.25.

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

Since Teva's Denosumab (TVB-009P) was developed as a biosimilar (application under Article 10(4) of Directive 2001/83/EC) to Prolia® (Amgen Europe B.V.), a tailored clinical program was justified.

As a part of the clinical development program, two studies have been conducted and completed: a Phase 1 PK/PD study in healthy participants (Study 10157) and a Phase 3 comparative efficacy and safety study in patients with postmenopausal osteoporosis (Study 30085).

SIV.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Study 10157, a Phase 1 PK/PD study in healthy participants, included 345 healthy adult male and female participants, aged between 28 and 55 years.

Study 30085, a Phase 3 comparative efficacy and safety study in patients with postmenopausal osteoporosis, included 332 female postmenopausal patients, aged between 60 and 84 years, with a diagnosis of osteoporosis.

Table 10: Important Exclusion Criteria

Exclusion criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
Exclusion criteria applicable for all studies			

Hypocalcaemia	Contraindication for denosumab use (Prolia® SmPC, 4.3).	No	Hypocalcaemia is a contraindication for denosumab therapy (Prolia® SmPC, 4.3). Hypocalcaemia must be corrected by adequate intake of calcium and vitamin D before initiating therapy (Prolia® SmPC, 4.4). Patients receiving denosumab must be adequately supplemented with calcium and vitamin D (Prolia® SmPC, 4.2). In line with the innovator's (Prolia®, Amgen) approach, Hypocalcemia is considered as an important identified risk in Teva's denosumab 60 mg/mL RMP.
Known hypersensitivity to any components of the investigational medicinal product or to calcium or vitamin D	Contraindication for denosumab use (SmPC, 4.3).	No	Hypersensitivity to the active substance or to any of the excipients is a contraindication for denosumab therapy (SmPC 4.3). In line with the innovator's (Prolia®, Amgen) approach, Hypersensitivity reactions are considered as an important identified risk in Teva's denosumab 60 mg/mL RMP.

Pregnant or lactating woman, or planning to become pregnant during the study	There are no or limited amount of data from the use of denosumab in pregnant women. Studies in animals have shown reproductive toxicity. It is unknown whether denosumab is excreted in human milk (Prolia® SmPC, 4.6).	No	Denosumab is not recommended for use in pregnant women and women of child-bearing potential not using contraception. Women should be advised not to become pregnant during and for at least 5 months after treatment with denosumab (Prolia® SmPC, 4.6). A decision on whether to abstain from breast-feeding or to abstain from therapy with denosumab should be made (Prolia® SmPC, 4.6).
Any medical condition that (treated or untreated), in the opinion of the investigator, could jeopardize or would compromise the participant's safety or ability to participate in the study	Pre-existing conditions may confound the study results.	No	An additional denosumab induced risk increase in these participants is not established.
History and/or presence of risk factors of osteonecrosis of the jaw	Osteonecrosis of the jaw has been reported rarely in patients receiving denosumab for osteoporosis (Prolia® SmPC, 4.4). The start of treatment should be delayed in patients with unhealed open soft tissue lesions in the mouth; an individual benefit-risk assessment is recommended prior to treatment with denosumab in patients with concomitant risk factors (Prolia® SmPC, 4.4). Pre-existing condition or risk factors may confound the study results.	No	In line with the innovator's (Prolia®, Amgen) approach, Osteonecrosis of the jaw is considered as an important identified risk in Teva's denosumab 60 mg/mL RMP.

Cardiac disease, as per investigator's discretion including electrocardiogram (ECG) abnormalities at screening	Cardiac disease, including ECG abnormalities, may pose significant risk of safety for participants in the study. In addition, pre-existing conditions may confound the study results.	No	In line with the innovator's (Prolia®, Amgen) approach, Cardiovascular events are considered as an important potential risk in Teva's denosumab 60 mg/mL RMP.
Malignancy or past malignancy (except for local non-melanoma skin cancer fully resected)	Pre-existing conditions may confound the safety profile evaluation of Teva's denosumab.	No	In line with the innovator's (Prolia®, Amgen) approach, Malignancy is considered as an important potential risk in Teva's denosumab 60 mg/mL RMP.
Current skin infection(s)	Patients receiving denosumab may develop skin infections (predominantly cellulitis) leading to hospitalisation (Prolia® SmPC, 4.4).	No	In line with the innovator's (Prolia®, Amgen) approach, Skin infection leading to hospitalisation is considered as an important identified risk in Teva's denosumab 60 mg/mL RMP.
Infectious disease (acute infection, any relevant chronic infection, ongoing hepatitis B, C, human immunodeficiency virus (HIV) infection, etc.)	Pre-existing infections may confound the study results.	No	In line with the innovator's (Prolia®, Amgen) approach, Infection is considered as an important potential risk in Teva's denosumab 60 mg/mL RMP.
Exclusion criteria applicable for study in patients with postmenopausal osteoporosis			
BMD (bone mineral density) T-score of less than -4.0	Not considered ethical to enrol such patients when approved therapies are available.	No	The safety and efficacy of denosumab is not expected to differ in patients with lower BMD T-scores.

Metabolic or bone disease (except osteoporosis) such as Paget's disease, Cushing's disease, rheumatoid arthritis, sclerosteosis, osteomalacia, osteogenesis imperfecta, osteopetrosis, ankylosing spondylitis, hyperprolactinemia, malabsorption syndrome, osteomyelitis, multiple myeloma or related lymphoproliferative disorder, or bone metastases	Other bone diseases such as Paget's disease, rheumatoid arthritis, osteogenesis imperfecta, as well as metabolic diseases could confound the efficacy results. Patients with multiple myeloma and bone metastases were evaluated in clinical studies conducted by the innovator for Xgeva® (Amgen), with a different dose and schedule (up to 120 mg monthly) (Xgeva® SmPC).	No	Denosumab 60 mg/mL solution for injection in pre-filled syringe is not indicated for use in these other patient populations.
History and/or presence of 1 severe or more than 2 moderate vertebral fractures	Pre-existing conditions may confound the study results.	No	In line with the innovator's (Prolia®, Amgen) approach, Fracture healing complications are considered as an important identified risk in Teva's denosumab 60 mg/mL RMP.
History and/or presence of hip fracture or atypical femur fracture	Atypical femoral fractures have been reported in patients receiving denosumab (Prolia® SmPC, 4.4). Atypical femoral fractures have also been reported in patients with certain co-morbid conditions (e.g. vitamin D deficiency, rheumatoid arthritis, hypophosphatasia) and with use of certain medicinal products (e.g. bisphosphonates, glucocorticoids, proton pump inhibitors) (Prolia® SmPC, 4.4). Pre-existing conditions may confound study results.	No	In line with the innovator's (Prolia®, Amgen) approach, Atypical femoral fracture is considered as an important identified risk in Teva's denosumab 60 mg/mL RMP.

Previous bisphosphonate treatment	Biphosphonates incorporate into bone and long-term use of bisphosphonates is associated with continued effects of the drug after the drug is discontinued; it was deemed appropriate to exclude previous bisphosphonate treatment.	No	Based on data from a transition study (alendronate to denosumab), conducted by innovator (Prolia®, Amgen), in postmenopausal women with osteoporosis the pharmacokinetics and pharmacodynamics of denosumab were not altered by previous alendronate therapy (Prolia® SmPC, 4.5).
Renal impairment manifested with an estimated glomerular filtration rate (eGFR) <45 mL/min	Treatment with antiresorptive agents reduces the ability to mobilize calcium from bone; thus, hypocalcaemia could be exacerbated in patients with renal impairment.	No	Patients with severe renal impairment (creatinine clearance < 30 mL/min) or receiving dialysis are at greater risk of developing hypocalcaemia. The risks of developing hypocalcaemia increase with increasing degree of renal impairment. Adequate intake of calcium, vitamin D and regular monitoring of calcium is especially important in these patients (Prolia® SmPC, 4.4). No dose adjustment is required in patients with renal impairment (Prolia®, SmPC 4.2).

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

Based on the number of exposed participants, the duration of participant exposure, the total dose of denosumab and the mechanism of action, Teva's denosumab clinical development program is not able to detect rare adverse drug reactions (ADRs), as well as ADRs associated with prolonged exposure or long latency.

SIV.3 Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

The influence of intrinsic factors (such as age, gender, race, region, or concomitant medications) on the adverse event profile of TVB-009P has not been evaluated in conducted studies.

Table 11: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
Pregnant women	Two pregnancies have been reported in the clinical development program. In study 10157, two pregnancies were reported during the trial: 1 biochemical pregnancy in the PROLIA® EU treatment group and 1 pregnancy in the TVB-009P treatment group that was diagnosed at the end of the trial and the outcome was considered recovered/resolved. The participant who reported biochemical pregnancy was considered as lost to follow-up (due to unsuccessful follow-up attempts) and the outcome of pregnancy was unknown. No participants had positive pregnancy test results during study 30085. There are no or limited amount of data from the use of denosumab in pregnant women and it is unknown whether denosumab is excreted in human milk (Prolia® SmPC, 4.6). According to the Prolia® SmPC, section 4.6, denosumab is not recommended for use in pregnant women and women of child-bearing potential not using contraception. Women should be advised not to become pregnant during and for at least 5 months after treatment with denosumab. A decision on whether to abstain from breast-feeding or to abstain from therapy with denosumab should be made.
Breastfeeding women	No cases of lactation have been reported in the clinical development program.
Patients with relevant comorbidities:	
• Patients with hepatic impairment	Not included in the clinical development program. According to the Prolia® SmPC, section 4.2, the safety and efficacy of denosumab have not been studied in patients with hepatic impairment.
• Patients with renal impairment	Not included in the clinical development program. According to the Prolia® SmPC, section 4.2, no dose adjustment is required in patients with renal impairment. No data is available in patients with severe renal impairment (glomerular filtration rate, GFR < 30 mL/min).In clinical studies with Prolia®, patients with severe renal impairment (creatinine clearance < 30 mL/min) or receiving dialysis were at greater risk of developing hypocalcaemia in the absence of calcium supplementation (Prolia® SmPC, section 4.8). The risks increase with increasing degree of renal impairment, and severe and fatal cases have been reported (Prolia® SmPC, section 4.4). Adequate intake of calcium, vitamin D and regular monitoring of calcium is especially important in in patients with severe renal impairment or receiving dialysis (Prolia® SmPC, sections 4.4 and 4.8).

<table>
<tr><td>

- Patients with cardiovascular impairment
- Immunocompromised patients
- Patients with a disease severity different from inclusion criteria in clinical trials

</td><td>Not included in the clinical development program.</td></tr>
<tr><td>Population with relevant different ethnic origin</td><td>

In Study 1015:

	TVB-009P (60 mg) N = 115 n (%)	**Prolia US (60 mg) N = 115 n (%)**	**Prolia EU (60 mg) N = 115 n (%)**
Race group			
White	103 (90)	97 (84)	107 (93)
Black or African American	12 (10)	18 (16)	8 (7)
Ethnicity			
Hispanic or Latino	115 (100)	115 (100)	114 (>99)
Not Hispanic or Latino	0	0	1 (<1)

In Study 30085, in the main treatment period:

	TVB 009P (60 mg) N = 166		**Prolia US (60 mg) N = 165**	
	Patients n (%)	**Patient-time (months)**	**Patients n (%)**	**Patient-time (months)**
Race group				
White	165 (99.4%)	1928.1	163 (98.8%)	1899.2
Black or African American	1 (0.6%)	12.5	1 (0.6%)	11.8
Not Reported or Unknown	0	0	1 (0.6%)	12.4
Ethnicity				
Hispanic or Latino	23 (13.9%)	266.6	18 (10.9%)	196.1
Not Hispanic or Latino	143 (86.1%)	1674	147 (89.1%)	1727.3

In Study 30085, in the transition period:

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<tr><td></td><td>
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<tr><th></th><th colspan="2">TVB 009P/TVB 009P
(60 mg/60 mg)
N = 148</th><th colspan="2">Prolia US/Prolia US
(60 mg/60 mg)
N = 72</th><th colspan="2">Prolia US/TVB 009P
(60 mg/60 mg)
N = 71</th></tr>
<tr><th></th><th>Patients n (%)</th><th>Patient-time (months)</th><th>Patients n (%)</th><th>Patient-time (months)</th><th>Patients n (%)</th><th>Patient-time (months)</th></tr>
<tr><td colspan="7">Race group</td></tr>
<tr><td>White</td><td>147 (99.3%)</td><td>857.8</td><td>71 (98.6%)</td><td>417.7</td><td>70 (98.6%)</td><td>414</td></tr>
<tr><td>Black or African American</td><td>1 (0.7%)</td><td>6.6</td><td>1 (1.4%)</td><td>5.4</td><td>0</td><td>0</td></tr>
<tr><td>Not Reported or Unknown</td><td>0</td><td>0</td><td>0</td><td>0</td><td>1 (1.4%)</td><td>5.8</td></tr>
<tr><td colspan="7">Ethnicity</td></tr>
<tr><td>Hispanic or Latino</td><td>21 (14.2%)</td><td>121.8</td><td>10 (13.9%)</td><td>59.2</td><td>4 (5.6%)</td><td>18.6</td></tr>
<tr><td>Not Hispanic or Latino</td><td>127 (85.8%)</td><td>742.6</td><td>62 (86.1%)</td><td>363.9</td><td>67 (94.4%)</td><td>401.2</td></tr>
</table>
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<tr><td>Subpopulations carrying relevant genetic polymorphisms</td><td>Not included in the clinical development program</td></tr>
<tr><td colspan="2">Other</td></tr>
<tr><td>• Paediatric patients</td><td>Not included in the clinical development program.
Therefore, there is no clinical trial experience with TVB-009P in paediatric population.
According to Prolia® (Amgen) SmPC, section 4.2, denosumab should not be used in children aged below18 years because of safety concerns of serious hypercalcaemia, and potential inhibition of bone growth and lack of tooth eruption. Further, in Prolia® clinical trials, some cases were complicated by acute renal injury (Prolia® SmPC, 4.4 and 4.8).</td></tr>
<tr><td>• Elderly patients</td><td>Since all patients in the study 30085 were aged between 60 and 84 years, clinical trial experience with TVB-009P in elderly patients is available. Of the 331 patients in the safety analysis set, 228 (69%) were aged ≥65 years.
The PK properties of TVB-009P and PROLIA® US were similar in the study 30085. According to the Prolia® SmPC, section 4.2, no dose adjustment is required in elderly (≥ 65 years) patients.</td></tr>
</table>

Part II: Module SV - Post-Authorisation Experience

Not applicable.

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

Potential for Misuse for Illegal Purposes

Based on the mechanism of action of TVB-009P, there is no indication to suggest a potential for abuse or dependence.

Part II: Module SVII - Identified and Potential Risks

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

TVB-009P was developed as a biosimilar to the reference product, Prolia® (Amgen). The safety concerns for the biosimilar are expected to be the same as those for Prolia®. No new safety concerns were identified in the clinical development program for TVB-009P.

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

Not applicable. The safety concerns for the biosimilar are expected to be the same as those for Prolia® (Amgen).

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

The list of safety concerns in Teva's denosumab RMP v1.1 is in line with the reference product's (Prolia®, Amgen) RMP v31.0, dated 11 January 2023, and published on 10 January 2024 on EMA's webpages.

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

Table 12: Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risk: Hypocalcaemia	
Potential mechanisms	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 3, randomized, double-blind, and placebo- or active-controlled studies of the originator (Prolia®, Amgen).
Characterisation of the risk	Frequency: In the study 30085, in the main treatment period, 3 participants in the TVB-009P treatment group (1.8%) and 1 participant in the Prolia® (US) treatment group (0.6%) experienced hypocalcaemia. All 3 events of hypocalcaemia in the TVB-009P treatment group were considered with reasonable possible relationship to the study drug, while the event

	in the Prolia® (US) treatment group was considered not related to the study drug. During the transition period, 1 participant in the Prolia® (US)/TVB-009P treatment group (1.4%) experienced hypocalcaemia. The event was considered not related to the study drug. There were no events of hypocalcaemia in other treatment groups. In addition, no events of hypocalcaemia were noted in the study 10157. According to Prolia® (Amgen) SmPC, hypocalcaemia is a rare adverse reaction with denosumab use (Prolia® SmPC 4.8). <u>Severity and reversibility of risk</u> In the study 30085, all events of hypocalcaemia were mild and non-serious. According to Prolia® (Amgen) SmPC, in the post-marketing setting, severe symptomatic hypocalcaemia (resulting in hospitalisation, life-threatening events, and fatal cases) has been reported; most cases occurred in the first weeks of initiating therapy, however, it has also occurred later (Prolia®, SmPC 4.4). In the post-marketing setting, rare cases of severe symptomatic hypocalcaemia resulting in hospitalisation, life-threatening events, and fatal cases have been reported, predominantly in patients at increased risk of hypocalcaemia receiving denosumab (Prolia®, SmPC 4.8). Clinical manifestations of severe symptomatic hypocalcaemia have included QT interval prolongation, tetany, seizures and altered mental status; in addition, symptoms of hypocalcaemia in Prolia® clinical studies included paraesthesias or muscle stiffness, twitching, spasms and muscle cramps (Prolia® SmPC, 4.8). Hypocalcaemia is reversible when treated with oral calcium and vitamin D supplementation. In severe cases, intravenous calcium supplementation may be required. <u>Long-term outcomes and impact on the quality of life</u> No long-term complications are anticipated for properly treated hypocalcaemia. For severe symptomatic hypocalcaemia, patients may be hospitalized for treatment. Generally, patients recover when their hypocalcaemia is treated.
Risk factors and risk groups	Risk factors include severe renal impairment and hyperphosphatemia. Patients with severe renal impairment (creatinine clearance < 30 mL/min) or receiving dialysis are at greater risk of developing hypocalcaemia, and the risks of developing hypocalcaemia and accompanying parathyroid hormone elevations increase with increasing degree of renal impairment; severe and fatal cases have been reported (Prolia® SmPC, 4.4). Concomitant glucocorticoid treatment is an additional risk factor for hypocalcaemia (Prolia® SmPC 4.4). 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, and some medications (Prolia® Canadian Product Monograph, Warnings and Precautions).

Preventability	Pre-existing hypocalcaemia must 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 before each dose and, in patients predisposed to hypocalcaemia within two weeks after the initial dose (SmPC, 4.4). If any patient presents with suspected symptoms of hypocalcaemia during treatment calcium levels should be measured, and patients should be encouraged to report symptoms indicative of hypocalcaemia (SmPC, 4.4).
Impact on the risk-benefit balance of the product	The risk of hypocalcaemia has been considered in the product benefit-risk assessment. In the light of the product labelling addressing this risk, the overall benefit-risk balance is considered to be positive.
Potential public health impact of safety concern	Significant public health impact is not expected as this risk is preventable and treatable with the appropriate routine risk minimisation measures communicated clearly in the SmPC.

Important Identified Risk: Skin Infection Leading to Hospitalisation	
Potential mechanisms	Keratinocytes can express RANKL and blocking RANKL in mice decreased the number of regulatory T-cells in skin, leading to an increased inflammatory response (Loser et al, 2006; Yamaguchi and Sakaguchi, 2006).
Evidence source(s) and strength of evidence	This risk was identified in the phase 3, randomized, double-blind, placebo- or active-controlled studies of the originator (Prolia®, Amgen).
Characterisation of the risk	Frequency: There were no reports of skin infection leading to hospitalization during the Study 30085 (or 10157). According to Prolia® SmPC, cellulitis is an uncommon adverse reaction with denosumab use (Prolia® SmPC, 4.8). Severity and reversibility of risk According to Prolia® SmPC, patients receiving denosumab may develop skin infections (predominantly cellulitis) leading to hospitalisation (Prolia® SmPC, 4.4). These events typically resolve with administration of antibiotics. Long-term outcomes and impact on the quality of life No long-term complications are anticipated for properly treated patients who are hospitalized due to skin infections. Although a hospital stay is required, 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, 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.
Preventability	No preventive measures are known. Patients should be advised to seek prompt medical attention if they develop signs or symptoms of cellulitis (SmPC, 4.4).
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. In the light of the product labelling addressing this risk, the overall benefit-risk balance is considered to be positive.
Potential public health impact of safety concern	Since frequency of skin infection leading to hospitalisation is relatively low, and the adverse events can be effectively treated by antibiotics, the negative impact to public health is relatively small.

Important Identified Risk: Osteonecrosis of the Jaw	
Potential mechanisms	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. Evidence supporting these hypotheses has been variable and little is understood in how these multiple pathways might interact (Fassio et al, 2017; Aghaloo et al, 2015).
Evidence source(s) and strength of evidence	This risk was identified in open-label long-term extensions to phase 3, and randomized, double-blind, placebo-controlled studies of the originator (Prolia®, Amgen).
Characterisation of the risk	<u>Frequency</u>: In the study 30085, in the main treatment period, in the Prolia® (US) treatment group, 1 participant developed osteonecrosis of the jaw (0.6 %) and 1 participant developed osteonecrosis (0.6 %). Both events were considered with reasonable possible relationship to Prolia® (US). There were no events of osteonecrosis in the other treatment groups. No events of osteonecrosis were observed in the transition period. In addition, no events of osteonecrosis were noted in study 10157. According to Prolia® SmPC, osteonecrosis of the jaw has been reported rarely in patients receiving denosumab for osteoporosis (Prolia® SmPC, 4.4 and 4.8). <u>Severity and reversibility of risk</u> In the study 30085, event of osteonecrosis of the jaw was mild, while the event of osteonecrosis was of moderate intensity. In general, ONJ events are clinically reversible with supportive care, antibiotics; however, surgical treatment may be required. <u>Long-term outcomes and impact on the quality of life</u> No data on long-term outcomes are available.

	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 (Mehrotra and Ruggiero, 2006; Ruggiero et al, 2006; Prolia® Canadian Product Monograph, Warnings and Precautions section).
Preventability	A dental examination with appropriate preventive dentistry is recommended prior to treatment with denosumab, especially in patients with risk factors. The start of treatment/new treatment course should be delayed in patients with unhealed open soft tissue lesions in the mouth (SmPC, 4.4). 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 (SmPC, 4.4).
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. Taking into account the product labelling and additional risk minimization measures (Patient Card) addressing this risk, the overall benefit-risk balance is considered to be positive.
Potential public health impact of safety concern	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.

Important Identified Risk: Hypersensitivity Reactions	
Potential mechanisms	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 Prolia® (Amgen) postmarketing setting based on a clinically plausible association between administration of denosumab and hypersensitivity reactions.
Characterisation of the risk	Frequency: In the study 30085, in the main treatment period, 2 participants in the Prolia® (US) treatment group (1.2%) experienced hypersensitivity reactions. One event was considered with a reasonable possible relationship to the study drug, while the other event was considered

	with no reasonable possible relationship to the study drug. There were no hypersensitivity reactions in other treatment groups. None of the participants developed hypersensitivity reactions during the transition period. In addition, no events of hypersensitivity reactions were noted in the study 10157. According to the Prolia® (Amgen) SmPC, drug hypersensitivity and anaphylactic reaction are rare adverse reactions with denosumab use (Prolia® SmPC, 4.8). <u>Severity and reversibility of risk</u> In the study 30085, both events of hypersensitivity reactions were mild and non-serious. According to Prolia® SmPC, in the post-marketing setting, rare events of drug-related hypersensitivity, including rash, urticaria, facial swelling, erythema, and anaphylactic reactions have been reported in patients receiving denosumab (SmPC, 4.8). Hypersensitivity reactions are generally reversible with discontinuation of the medication, however, treatment may be required. <u>Long-term outcomes and impact on the quality of life</u> No long-term complications are anticipated for properly treated hypersensitivity reactions. 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 (SmPC, 4.3).
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 section 4.3.
Impact on the risk-benefit balance of the product	The risk of hypersensitivity reactions has been considered in the product benefit-risk assessment. In the light of the product labelling addressing this risk, the overall benefit-risk balance is considered to be positive.
Potential public health impact of safety concern	No significant public health impact is expected as reports of severe events (e.g., anaphylaxis) are rare.

Important Identified Risk: Atypical Femoral Fracture	
Potential mechanisms	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 (Ismail et al, 2018; Shane et al, 2010; Prolia® SmPC, 4.4).
Evidence source(s) and strength of evidence	This risk was identified in an open-label long-term extension to phase 3, randomized, double-blind, active-controlled study for the originator (Prolia®, Amgen).
Characterisation of the risk	Frequency: There were no reports of atypical femoral fracture during the Study 30085 (or 10157). According to Prolia® (Amgen) SmPC, atypical femoral fractures have been reported rarely in patients receiving denosumab (Prolia® SmPC, 4.8). Severity and reversibility of risk According to Prolia® (Amgen) SmPC, atypical femoral fractures may occur with little or no trauma in the subtrochanteric and diaphyseal regions of the femur, they are often bilateral, and characterised by specific radiographic findings (Prolia® SmPC, 4.4). Atypical femoral fracture is 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 and impact on the quality of life No data on long-term outcomes are available. 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 (Bubbear et al, 2016).
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 (Meier et al, 2013; Giusti et al, 2011). Atypical femoral fractures have also been reported in patients with certain comorbid conditions (e.g., vitamin D deficiency, rheumatoid arthritis, hypophosphatasia) and with use of bisphosphonates, glucocorticoids, and proton pump inhibitors (Shane et al, 2010; Prolia® SmPC, 4.4).
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. During denosumab treatment, patients should be advised to report new or unusual thigh, hip, or groin pain; patients presenting with such symptoms should be evaluated for an incomplete femoral fracture (SmPC, 4.4).
Impact on the risk-benefit balance of the product	The risk of atypical femoral fracture has been considered in the product benefit-risk assessment. In the light of the product labelling addressing this risk, the overall benefit-risk balance is considered to be positive.
Potential public health impact of safety concern	Based on the infrequency of AFF in patients treated with denosumab, no significant additional public health impact is expected.

Important Identified Risk: Hypercalcemia in Paediatric Patients Receiving Denosumab and After Treatment Discontinuation	
Potential mechanisms	The exact mechanism of hypercalcemia following treatment discontinuation in the growing skeleton 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 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.
Evidence source(s) and strength of evidence	Data to evaluate safety concern were derived from originator's (Prolia®, Amgen) clinical trials in paediatric patients with osteogenesis imperfecta, XGEVA® (Amgen) clinical studies, and postmarketing adverse event reporting involving paediatric patients receiving denosumab at unapproved doses and/or unapproved indications for use (for originator).
Characterisation of the risk	Frequency: Paediatric patients were excluded from TVB-009P clinical development program. Severity and reversibility of risk According to Prolia® (Amgen) SmPC, serious hypercalcaemia has been reported in paediatric patients; some cases were complicated by acute renal injury (Prolia® SmPC, 4.4 and 4.8). Long-term outcomes and impact on the quality of life Paediatric patients may present with severe hypercalcemia requiring hospitalization. Generally, patients recover when the hypercalcemia is treated.
Risk factors and risk groups	Paediatric patients with growing skeletons and high bone turnover disease states (such as osteogenesis imperfecta).
Preventability	Denosumab is not indicated in paediatric patients (age < 18 years) and should not be used in paediatric patients (SmPC, 4.2).
Impact on the risk-benefit balance of the product	The benefit-risk profile of denosumab is not favourable in the paediatric patient population.

Potential public health impact of safety concern	No significant impact on the public health is expected since it is clearly communicated in the SmPC that denosumab should not be used in population below 18 years of age (SmPC, 4.2).

Important Potential Risk: Fracture Healing Complications	
Potential mechanisms	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 potential mechanism of action.
Characterisation of the risk	Frequency: There were no reports of fracture healing complications during the Study 30085 (or 10157). Severity and reversibility of risk This risk has not been substantiated; however, the effects of denosumab on osteoclasts are fully reversible. Long-term outcomes and impact on the quality of life This risk has not been substantiated; however, no long-term impact would be anticipated based on reversibility. 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 (Hernandez et al, 2012; Gaston and Simpson, 2007).
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.
Potential public health impact of safety concern	No significant impact on public health is anticipated.

Important Potential Risk: Infection	
Potential mechanisms	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 bone mineral density (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 of the originator (Prolia®, Amgen).
Characterisation of the risk	Frequency: In the study 10157, 3 participants in the TVB-009P treatment group (3%), 1 participant in the Prolia® (US) treatment group (<1%) and 3 participants in the Prolia® (EU) treatment group (3%) experienced infections (SOC Infections and infestations). No events were considered related to the study drug. In the study 30085, in the main treatment period, 40 participants in the TVB-009P treatment group (24.1%) and 46 participants in the Prolia® (US) treatment group (27.9%) experienced infections (SOC Infections and infestations). COVID-19 and nasopharyngitis were most frequently reported. Only 3 events of urinary tract infections, 1 event in TVB-009P treatment group and 2 events in Prolia® (US) treatment group, were considered related to the study drug; all other events of infections were considered not related to treatment. During the transition period, 16 participants in the TVB-009P/TVB-009P treatment group (10.8%), 9 participants in Prolia® (US)/Prolia® (US) treatment group (12.5%) and 7 participants in the Prolia® (US)/TVB-009P treatment group (9.9%) experienced infections (SOC Infections and infestations). Nasopharyngitis, upper respiratory tract infection and COVID-19 were most frequently reported. No events of infections were considered related to the study drug. According to the Prolia® (Amgen) SmPC, urinary tract infections and upper respiratory tract infections are common adverse reactions with denosumab use, while diverticulitis and ear infections are uncommon (Prolia® SmPC, 4.8). Severity and reversibility of risk In the study 10157, all events of infections were of moderate intensity and non serious. In the study 30085, in the main treatment period, as well as in transition period, all events of infections were of mild or moderate intensity. In the main treatment period, 2 participants in the TVB-009P treatment group (1.2%) and 1 participant in the Prolia® (US) treatment group (0.6%) experienced serious infections. During the transition period, 2 participants in the TVB-009P/TVB-009P treatment group (1.4%) experienced serious infections. There were no events of serious infections in other treatment groups. Infections when treated appropriately are generally reversible. Long-term outcomes and impact on the quality of life Infection generally responds to appropriate treatment and as such no long-term effects are anticipated. 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.
Potential public health impact of safety concern	No significant public health impact is expected for this unsubstantiated risk as effective treatments are available.

Important Potential Risk: Cardiovascular Events	
Potential mechanisms	Elevated levels of osteoprotegerin (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 the study 10157, 1 participant in the Prolia® (EU) treatment group (<1%) experienced cardiac event (SOC Cardiac disorders; the participant experienced supraventricular arrhythmia). No participants experienced vascular events (SOC Vascular disorders). In addition, 1 participant in the Prolia® (US) treatment group (<1%) and 1 participant in the Prolia® (EU) treatment group (<1%) experienced increased blood pressure. Also, 1 participant in the TVB-009 treatment group (<1%) and 1 participant in the Prolia® (US) treatment group experienced presyncope. No events were considered related to the study drug. In the study 30085, in the main treatment period, 3 participants in the TVB-009 treatment group (1.8%) and 3 participants in the Prolia® (US) treatment group (1.8%) experienced cardiac events (SOC Cardiac disorders), while 14 participants in the TVB-009 treatment group (8.4%) and 10 participants in the Prolia® (US) treatment group (6.1%) experienced vascular events (SOC Vascular disorders). In addition, 3 participants in the TVB-009 treatment group (1.8%) and 2 participants in the Prolia® (US) treatment group (1.2%) experienced increased blood pressure. Only one event of hypertension (in the Prolia® (US) treatment group) was considered related to the study drug; all other events were considered not related to the study drug. During the transition period, 3 participants in the TVB-009/TVB-009 treatment group (2.0%) experienced cardiac events (SOC Cardiac disorders), while 2 participants in the same treatment group (1.4%) experienced vascular events (SOC Vascular disorders). In addition, 1 participant in the Prolia® (US)/Prolia® (US) treatment group (1.4%) experienced abnormal blood pressure. Also, 1 participant in the TVB-009/TVB-009 treatment group (0.7%) experienced syncope. No events were considered related to the study drug.

	<u>Severity and reversibility of risk</u> In the study 10157, majority of cardiac and vascular events were mild; one event of presyncope was moderate. All events were non-serious. In the study 30085, in the main treatment period, as well as in transition period, all cardiac events (SOC Cardiac disorders) and vascular events (SOC Vascular disorders) were mild or moderate; there were no severe events In the main treatment period, 1 participant in the Prolia® (US) treatment group (0.6%) experienced serious cardiac events (SOC Cardiac disorders; the patient experienced atrial flutter and myocardial ischaemia), while 1 participant in the TVB-009 treatment group (0.6%) experienced serious vascular event (SOC Vascular disorders; the patient experienced peripheral arterial occlusive disease). During the transition period, no participants experienced serious cardiovascular events. This risk has not been substantiated; however, cardiovascular events may be severe/life-threatening. Effects of denosumab to block RANKL are fully reversible. <u>Long-term outcomes and impact on the quality of life</u> This risk has not been substantiated; however, cardiovascular events could impact patient long-term outcome. Cardiovascular events vary greatly in severity. For severe events, 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 (Schulz et al, 2004; Hak et al, 2000). 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, 2007; Smith et al, 2004).
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 in the indicated populations.
Potential public health impact of safety concern	No significant impact of denosumab on public health (with regards to cardiovascular disease severity or incidence) is anticipated for this unsubstantiated risk.

Important Potential Risk: Malignancy	
Potential mechanisms	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 tumour types provide no evidence for carcinogenic risk associated with RANKL inhibition (Armstrong et

	al, 2008; Jones et al, 2006; Mori et al, 2007). In in vivo rodent cancer models, RANKL inhibition has been shown to have a beneficial effect (Vanderkerken et al, 2003; Yonou et al, 2003; Zhang et al, 2001). 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 the 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 study 10157, there were no reports of malignancies. In the study 30085, in the main treatment period, 1 participant in the TVB-009P treatment group (0.6%) developed adrenal mass, 1 participant in the same treatment group (0.6%) developed gastric neoplasm, 1 participant in the Prolia® (US) treatment group (0.6%) developed splenic marginal zone lymphoma, and 1 participant in the same treatment group (0.6%) developed squamous cell carcinoma. No events were considered related to the study drug. During the transition period, 1 participant in the TVB-009P/TVB-009P treatment group (0.7%) developed bone cancer, and 1 participant in the Prolia® (US)/TVB-009 treatment group (1.4%) developed skin neoplasm. No events were considered related to the study drug. Severity and reversibility of risk In the study 30085, in the main treatment period, the event of gastric neoplasm was mild, the events of splenic marginal zone lymphoma and squamous cell carcinoma were moderate, while the event of adrenal mass was of severe intensity. During the transition period, the event of skin neoplasm was of mild intensity, while the event of bone cancer was severe. Malignancy is a clinically important event requiring medical intervention. 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 and impact on the quality of life New primary malignancy or progression of existing malignancy may be fatal, life-threatening and long-term outcomes will likely be impacted. Malignancy can be life-threatening and generally requires intervention e.g., surgery, radiation, and/or chemotherapy.
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, 2008; WHO, 2010).

Preventability	No preventive measures are known.
Impact on the risk-benefit balance of the product	The potential risk of malignancy has been considered in overall assessment supporting a positive benefit-risk profile in the indicated populations.
Potential public health impact of safety concern	No significant impact on public health is anticipated.

Part II: Module SVIII - Summary of the Safety Concerns

Table 13: Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	• Hypocalcaemia • Skin infection leading to hospitalisation • Osteonecrosis of the jaw • Hypersensitivity reactions • Atypical femoral fracture • Hypercalcemia in paediatric 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 reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires:

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

Table 14: List of Questionnaires

Safety concern for which the questionnaire is used	Purpose	Trigger events*
Hypocalcaemia	Specific adverse reaction follow-up questionnaire: Denosumab – Hypocalcaemia questionnaire v1.0 To follow-up and collect in more details information to further characterise safety concern of hypocalcaemia.	PTs: Hypocalcaemia; Blood calcium decreased
Skin infection leading to hospitalisation	Specific adverse reaction follow-up questionnaire: Denosumab – Infection questionnaire v1.0 To follow-up and collect in more details information to further characterise safety concerns of skin infection leading to hospitalisation and infections (of any type).	SOC Infections and infestations
Infection		
Osteonecrosis of the jaw	Specific adverse reaction follow-up questionnaire: Denosumab – Osteonecrosis of the jaw questionnaire v1.0 To follow-up and collect in more details information to further characterise safety concern of osteonecrosis of the jaw.	PT Osteonecrosis of jaw
Atypical femoral fracture	Specific adverse reaction follow-up questionnaire: Denosumab – Atypical fractures questionnaire v1.0 To follow-up and collect in more details information to further characterise safety concern of atypical femoral fracture.	PTs Atypical femur fracture; Atypical fracture

Fracture healing complications	Specific adverse reaction follow-up questionnaire: Denosumab – Fracture healing questionnaire v1.0 To follow-up and collect in more details information to further characterise safety concern of atypical femoral fracture.	PTs: Fracture delayed union; Fracture nonunion; Fracture malunion; Pseudarthrosis.
Malignancy	Specific adverse reaction follow-up questionnaire: Denosumab – Malignancy questionnaire v1.0 To follow-up and collect in more details information to further characterise safety concern of malignancy.	SMQ Malignancies
Hypersensitivity reactions	Specific adverse reaction follow-up questionnaire: Denosumab – Hypersensitivity questionnaire v1.0 To follow-up and collect in more details information to further characterise safety concern of hypersensitivity reactions.	SMQ Hypersensitivity (narrow scope)

*List of trigger terms is displayed according to MedDRA version 27.1 and will be updated with MedDRA version upgrades as needed to accommodate any relevant changes.

III.2 Additional Pharmacovigilance Activities

Not applicable.

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

The safety information in the proposed product information is aligned to the reference medicinal product.

V.1. Routine Risk Minimisation Measures

Table 15: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation measures
IMPORTANT IDENTIFIED RISKS	
Hypocalcaemia	**Routine risk communication:** Risk is addressed in SmPC sections 4.2, 4.3, 4.4, and 4.8. Described in PL sections 2, 3 and 4. **Routine risk minimisation measures recommending specific clinical measures to address the risk:** Recommendation for correction of hypocalcaemia prior to initiating treatment with denosumab and clinical monitoring of calcium levels during treatment with denosumab is included in SmPC Section 4.4. **Other routine risk minimisation measures beyond the Product Information:** Legal status: Prescription only medicine.
Skin infection leading to hospitalisation	**Routine risk communication:** Risk is addressed in SmPC sections 4.4 and 4.8. Described in PL sections 2 and 4. **Routine risk minimisation measures recommending specific clinical measures to address the risk:** Patients should be advised to seek prompt medical attention if they develop signs or symptoms of cellulitis (SmPC section 4.4). **Other routine risk minimisation measures beyond the Product Information:** Legal status: Prescription only medicine.

Safety concern	Routine risk minimisation measures
Osteonecrosis of the jaw	**Routine risk communication:** Risk is addressed in SmPC sections 4.4, 4.8 and 5.1. Described in PL sections 2 and 4. **Routine risk minimisation measures 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 osteonecrosis of the jaw occurs is included in SmPC Section 4.4. **Other routine risk minimisation measures beyond the Product Information:** Legal status: Prescription only medicine.
Hypersensitivity reactions	**Routine risk communication:** Risk is addressed in SmPC sections 4.3 and 4.8. Described in PL sections 2 and 4. **Routine risk minimisation measures recommending specific clinical measures to address the risk:** None. **Other routine risk minimisation measures beyond the Product Information:** Legal status: Prescription only medicine.
Atypical femoral fracture	**Routine risk communication:** Risk is addressed in SmPC sections 4.4, 4.8 and 5.1. Described in PL sections 2 and 4. **Routine risk minimisation measures recommending specific clinical measures to address the risk:** During denosumab treatment, patients should be advised to report new or unusual thigh, hip, or groin pain; patients presenting with such symptoms should be evaluated for an incomplete femoral fracture (SmPC section 4.4). **Other routine risk minimisation measures beyond the Product Information:** Legal status: Prescription only medicine.
Hypercalcemia in paediatric patients receiving denosumab and after treatment discontinuation	**Routine risk communication:** Risk is addressed in SmPC sections 4.2, 4.4, 4.8 and 5.1. **Routine risk minimisation measures recommending specific clinical measures to address the risk:** None. **Other routine risk minimisation measures beyond the Product Information:** Legal status: Prescription only medicine.

Safety concern	Routine risk minimisation measures
IMPORTANT POTENTIAL RISKS	
Fracture healing complications	**Routine risk communication:** Risk is addressed in SmPC section 5.3. **Routine risk minimisation measures recommending specific clinical measures to address the risk:** None. **Other routine risk minimisation measures beyond the Product Information:** Legal status: Prescription only medicine.
Infection	**Routine risk communication:** Risk is addressed in SmPC section 4.8. Described in PL section 4. **Routine risk minimisation measures recommending specific clinical measures to address the risk:** None. **Other routine risk minimisation measures beyond the Product Information:** Legal status: Prescription only medicine.
Cardiovascular events	**Routine risk communication:** None. **Routine risk minimisation measures recommending specific clinical measures to address the risk:** None. **Other routine risk minimisation measures beyond the Product Information:** Legal status: Prescription only medicine.
Malignancy	**Routine risk communication:** None. **Routine risk minimisation measures recommending specific clinical measures to address the risk:** None. **Other routine risk minimisation measures beyond the Product Information:** Legal status: Prescription only medicine.
MISSING INFORMATION	
None	

V.2. Additional Risk Minimisation Measures

Table 16: Patient Card

Objectives	Patient card will be provided to address the following risk: • Osteonecrosis of the jaw
Rationale for the additional risk minimisation activity	The purpose of the patient card is to remind patients about important safety information that they need to be aware of before and during treatment with denosumab for osteoporosis and bone loss, including: • the risk of osteonecrosis of the jaw during treatment with denosumab; • 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 denosumab and to contact their doctor or dentist if problems with the mouth or teeth occur during treatment.
Target audience and planned distribution path	Target audience will be the patients. The patient card will be distributed to prescribers with instruction to provide it to patients. The methods for dissemination and the target audience in each Member State will be agreed at the national level by the respective competent authority of the Member State.
Plans to evaluate the effectiveness of the interventions and criteria for success	The success of proposed additional risk minimization activities will be measured by: • monitoring process indicator – risk minimization tool implementation. The implementation will be considered successful if MAH fulfilled obligation(s). o The distribution of the patient card will be tracked to ensure that it is distributed in accordance with the plan agreed with national agencies. • potential occurrence in the relevant cases. The ARMMs will be considered successful if no significant occurrence in the period after ARMMs implementation, without an alternative explanation, is noticed. Results of effectiveness evaluation will be presented in periodic reports.

V.3. Summary of Risk Minimisation Measures

Table 17: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
IMPORTANT IDENTIFIED RISKS		
Hypocalcaemia	**Routine risk minimisation measures:** SmPC section 4.4, where recommendation regarding correction and monitoring of calcium levels is provided. SmPC sections 4.2, 4.3, 4.4 and 4.8. PL sections 2, 3 and 4. Prescription only medicine. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse reaction follow-up questionnaire: Denosumab – Hypocalcaemia questionnaire v1.0 **Additional pharmacovigilance activities:** None.
Skin infection leading to hospitalisation	**Routine risk minimisation measures:** SmPC section 4.4, where instruction to advise patients to seek prompt medical attention if they develop signs or symptoms of cellulitis is provided. SmPC sections 4.4 and 4.8. PL sections 2 and 4. Prescription only medicine. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse reaction follow-up questionnaire: Denosumab – Infection questionnaire v1.0 **Additional pharmacovigilance activities:** None.
Osteonecrosis of the jaw	**Routine risk minimisation measures:** SmPC section 4.4, where oral hygiene and dental management guidance is provided. SmPC sections 4.4, 4.8 and 5.1. PL sections 2 and 4. Prescription only medicine. **Additional risk minimisation measures:** Patient card.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse reaction follow-up questionnaire: Denosumab – Osteonecrosis of the jaw questionnaire v1.0 **Additional pharmacovigilance activities:** None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Hypersensitivity reactions	**Routine risk minimisation measures:** SmPC sections 4.3 and 4.8. PL sections 2 and 4. Prescription only medicine. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse reaction follow-up questionnaire: Denosumab – Hypersensitivity questionnaire v1.0 **Additional pharmacovigilance activities:** None.
Atypical femoral fracture	**Routine risk minimisation measures:** SmPC section 4.4, where recommendation for reporting potential symptoms is provided. SmPC sections 4.4, 4.8 and 5.1. PL sections 2 and 4. Prescription only medicine. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse reaction follow-up questionnaire: Denosumab – Atypical fractures questionnaire v1.0 **Additional pharmacovigilance activities:** None.
Hypercalcemia in paediatric patients receiving denosumab and after treatment discontinuation	**Routine risk minimisation measures:** SmPC sections 4.2, 4.4, 4.8 and 5.1. Prescription only medicine. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
IMPORTANT POTENTIAL RISKS		
Fracture healing complications	**Routine risk minimisation measures:** SmPC section 5.3. Prescription only medicine. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse reaction follow-up questionnaire: Denosumab - Fracture healing questionnaire v1.0 **Additional pharmacovigilance activities:** None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Infection	**Routine risk minimisation measures:** SmPC section 4.8. PL section 4. Prescription only medicine. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse reaction follow-up questionnaire: Denosumab – Infection questionnaire v1.0 **Additional pharmacovigilance activities:** None.
Cardiovascular events	**Routine risk minimisation measures:** Prescription only medicine. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Malignancy	**Routine risk minimisation measures:** Prescription only medicine. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse reaction follow-up questionnaire: Denosumab – Malignancy questionnaire v1.0 **Additional pharmacovigilance activities:** None.
MISSING INFORMATION		
None		

Part VI: Summary of the Risk Management Plan

Summary of Risk Management Plan for Ponlimsi (Denosumab 60 mg/mL solution for injection)

This is a summary of the risk management plan (RMP) for Ponlimsi (Denosumab 60 mg/mL solution for injection; herein after also referred to as Ponlimsi). The RMP details important risks of Ponlimsi, how these risks can be minimised, and how more information will be obtained about Ponlimsi's risks and uncertainties (missing information).

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

This summary of the RMP for Ponlimsi 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 Ponlimsi's RMP.

I. The Medicine and What It is used for

Ponlimsi (Denosumab 60 mg/mL solution for injection) 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 60 mg as the active substance and it is given by subcutaneous injection.

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

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

Important risks of Ponlimsi, together with measures to minimise such risks and the proposed studies for learning more about Ponlimsi’s risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

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

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

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

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

II.A List of Important Risks and Missing Information

Important risks of Ponlimsi are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Ponlimsi. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table 18: Summary of Safety Concerns

List of important risks and missing information	
Important identified risks	• Hypocalcaemia • Skin infection leading to hospitalisation • Osteonecrosis of the jaw • Hypersensitivity reactions • Atypical femoral fracture • Hypercalcemia in paediatric 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

The safety information in the proposed product information is aligned to the reference medicinal product.

Table 19: Summary of Pharmacovigilance Activities and Additional Risk Minimisation Activities by Safety Concern

Important identified risk: Hypocalcaemia	
Evidence for linking the risk to the medicine	This risk was identified in the phase 3, randomized, double-blind, and placebo- or active-controlled studies of the originator (Prolia®, Amgen).
Risk factors and risk groups	Risk factors include severe renal impairment and hyperphosphatemia. Patients with severe renal impairment (creatinine clearance < 30 mL/min) or receiving dialysis are at greater risk of developing hypocalcaemia, and the risks of developing hypocalcaemia and accompanying parathyroid hormone elevations increase with increasing degree of renal impairment; severe and fatal cases have been reported (Prolia® SmPC, 4.4). Concomitant glucocorticoid treatment is an additional risk factor for hypocalcaemia (Prolia® SmPC 4.4). 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, and some medications (Prolia® Canadian Product Monograph, Warnings and Precautions).
Risk minimisation measures	Routine risk minimisation measures SmPC section 4.4, where recommendation regarding correction and monitoring of calcium levels is provided. SmPC sections 4.2, 4.3, 4.4 and 4.8. PL sections 2, 3 and 4. Prescription only medicine. Additional risk minimisation measures None.
Important identified risk: 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 of the originator (Prolia®, Amgen).
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 minimisation measures SmPC section 4.4, where instruction to advise patients to seek prompt medical attention if they develop signs or symptoms of cellulitis is provided. SmPC sections 4.4, and 4.8. PL sections 2 and 4. Prescription only medicine. Additional risk minimisation measures None.

Important identified risk: Osteonecrosis of the jaw	
Evidence for linking the risk to the medicine	This risk was identified in open-label long-term extensions to phase 3, and randomized, double-blind, placebo-controlled studies of the originator (Prolia®, Amgen).
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 (Mehrotra and Ruggiero, 2006; Ruggiero et al, 2006; Prolia® Canadian Product Monograph, Warnings and Precautions section).
Risk minimisation measures	Routine risk minimisation measures SmPC Section 4.4, where oral hygiene and dental management guidance is provided. SmPC sections 4.4, 4.8 and 5.1. PL sections 2 and 4. Prescription only medicine. Additional risk minimisation measures Patient card.
Important identified risk: Hypersensitivity reactions	
Evidence for linking the risk to the medicine	This risk was identified in the Prolia® (Amgen) postmarketing setting based on a clinically plausible association between administration of denosumab and hypersensitivity reactions.
Risk factors and risk groups	Known hypersensitivity to denosumab and any of its excipients (SmPC, 4.3).
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.3 and 4.8. PL sections 2 and 4. Prescription only medicine. Additional risk minimisation measures None.
Important identified risk: Atypical Femoral Fracture	
Evidence for linking the risk to the medicine	This risk was identified in an open-label long-term extension to phase 3, randomized, double-blind, active-controlled study for the originator (Prolia®, Amgen).
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 (Meier et al, 2013; Giusti et al, 2011). Atypical femoral fractures have also been reported in patients with certain comorbid conditions (e.g., vitamin D deficiency, rheumatoid arthritis, hypophosphatasia) and with use of bisphosphonates, glucocorticoids, and proton pump inhibitors (Shane et al, 2010; Prolia® SmPC, 4.4).

Risk minimisation measures	Routine risk minimisation measures SmPC section 4.4, where recommendation for reporting potential symptoms is provided. SmPC sections 4.4, 4.8 and 5.1. PL sections 2 and 4. Prescription only medicine. Additional risk minimisation measures None.
Important identified risk: Hypercalcemia in paediatric patients receiving denosumab and after treatment discontinuation	
Evidence for linking the risk to the medicine	Data to evaluate safety concern were derived from originator's (Prolia®, Amgen) clinical trials in paediatric patients with osteogenesis imperfecta, XGEVA® (Amgen) clinical studies, and postmarketing adverse event reporting involving paediatric patients receiving denosumab at unapproved doses and/or unapproved indications for use (for originator).
Risk factors and risk groups	Paediatric patients with growing skeletons and high bone turnover disease states (such as osteogenesis imperfecta).
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.2, 4.4, 4.8 and 5.1. PL section 2. Prescription only medicine. Additional risk minimisation measures None.
Important potential risk: 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 (Hernandez et al, 2012; Gaston and Simpson, 2007).
Risk minimisation measures	Routine risk minimisation measures SmPC section 5.3. Prescription only medicine. Additional risk minimisation measures None.
Important potential risk: 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 of the originator (Prolia®, Amgen).
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 minimisation measures SmPC section 4.8. PL section 4. Prescription only medicine. Additional risk minimisation measures None.
Important potential risk: Cardiovascular events	
Evidence for linking the risk to the medicine	This is a theoretical risk based on epidemiological data demonstrating elevated OPG 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 (Schulz et al, 2004; Hak et al, 2000). 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, 2007; Smith et al, 2004).
Risk minimisation measures	Routine risk minimisation measures Prescription only medicine. Additional risk minimisation measures None.
Important potential risk: Malignancy	
Evidence for linking the risk to the medicine	This is considered a potential risk based on the 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, 2008; WHO, 2010).
Risk minimisation measures	Routine risk minimisation measures Prescription only medicine. Additional risk minimisation measures None.

II.C Post-Authorisation Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Ponlimsi.

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

There are no studies required for Ponlimsi.

Part VII: Annexes

Table of contents

Annex 4 – Specific Adverse Drug Reaction Follow-Up Forms

Follow-up forms

- Denosumab – Hypocalcaemia questionnaire v1.0
- Denosumab – Infection questionnaire v1.0
- Denosumab – Osteonecrosis of the jaw questionnaire v1.0
- Denosumab – Atypical fractures (low energy, subtrochanteric/femoral shaft fractures) questionnaire v1.0
- Denosumab – Fracture healing questionnaire v1.0
- Denosumab – Malignancy questionnaire v1.0
- Denosumab – Hypersensitivity questionnaire v1.0

Denosumab – Hypocalcaemia questionnaire v1.0

- Supplement to the (S)AE Form -

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

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

PATIENT INFORMATION:

Age: .....

Gender: ☐M ☐F Pregnant: ☐Y ☐ N

Height ..... cm/ ..... in Weight ..... kg/ ..... lbs

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

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

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 subcutaneously (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 .....

ADVERSE EVENT DATA

Event reported term:.....

Event onset date (dd/mm/yyyy):.....

SIGNS AND SYMPTOMS (check all that apply)

☐ Numbness

Specify if involving digits and/or peri-oral region .....

☐ Convulsions

☐ Muscle twitching

☐ Muscle cramping

☐ Paraesthesia

☐ Syncope

☐ Tetany

☐ None

☐ Other .....

DIAGNOSIS (check all that apply)

Serum calcium at the time of event: .....mg/dL ☐Unknown

Please provide serum albumin result: .....

Serum albumin at the time of event < 4.0 g/dL?

☐Yes ☐No ☐Unknown

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

Serum creatinine at the time of event was > 2.0 X times upper limit of normal?

☐Yes ☐No ☐Unknown

(Please provide result) .....

Hypocalcaemia-induced EKG changes (QT prolongation)?

☐Yes ☐No ☐Unknown

TREATMENT:

Treated only as an outpatient? ☐Yes ☐No ☐Unknown
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: ☐ ≤ 1 day ☐ > 1 day ☐ ≤ 7 days ☐ > 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:.....

Hypocalcaemic Event Resolved ☐Yes ☐No ☐Unknown
If yes, on what date? (DD/MM/YYYY) .....

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 parathyroid disease .....
☐ History of malignancy (please specify) .....
☐ Hyperphosphatemia .....
☐ Recent surgery .....
☐ History of chronic renal disease .....
☐ History of hypoalbuminemia .....
☐ Hypoproteinemia .....
☐ Magnesium deficiency .....

☐ 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 hypocalcaemia event:

.....

☐ Prior hypocalcaemia event (before Denosumab treatment)
Please provide dates and details of prior hypocalcaemia event:

.....

Medication 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?

☐ Yes ☐ No ☐ Unknown (Please provide dose and dates) .....

.....

Taking calcium supplement?

☐ Yes ☐ No ☐ Unknown (Please provide dose and dates) .....

.....

☐ Other concomitant medications .....

Please give any additional information or comments you consider relevant and have not been covered by the questionnaire:

.....

.....

.....

.....

.....

REPORTER INFORMATION

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

Name and title:.....

Affiliation:.....

Address:.....

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

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

Signature: .....

Denosumab – Infection questionnaire v1.0

- Supplement to the (S)AE Form -

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

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

PATIENT INFORMATION:

Age: .....

Gender: ☐M ☐F Pregnant: ☐Y ☐ N

Height ..... cm/ ..... in Weight ..... kg/ ..... lbs

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

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

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 subcutaneously (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 .....

ADVERSE EVENT DATA

Event reported term:.....

Event onset date (dd/mm/yyyy):.....

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 .....

☐ Diarrhoea .....

☐ 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 (bacteraemia and/or sepsis)

☐ Other .....

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

Diagnostic	**Results / Units**	**Reference range/ Units**	**Date (dd/mm/ yyyy)**	**Report attached Y/N**	**Diagnostic**	**Results/ Units**	**Reference range/ Units**	**Date (dd/mm /yyyy)**	**Report attached Y/N**
Results at BASELINE (prior to Teva's denosumab)					**Results at TIME OF EVENT**				

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

Check which infection applies

☐Cardiac infections

- ☐ Endocarditis .....
- ☐ Pericarditis (purulent; tuberculous) .....
- ☐ Other, please specify: .....

☐ Ear and labyrinth infections

- ☐ Otitis media .....
- ☐ Otitis externa .....
- ☐ Other, please specify: .....

☐ Gastrointestinal/abdominal 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 .....
- ☐ Legionella pneumonia .....
- ☐ Mycoplasma pneumonia .....
- ☐ Other, please specify .....

☐Kidney and genito-urinary tract infections

- ☐ Cystitis .....
- ☐ Pyelonephritis .....
- ☐Urinary tract infection .....
- ☐Other, please specify: .....

☐ Systemic infections

- ☐ Bacteraemia .....
- ☐ 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 infections, please specify: .....

☐ Parasitic evaluation (ova, etc.) .....

DIAGNOSTICS

☐ Cultures done ☐ No ☐ Yes ☐Unknown

If yes, check which apply:

☐ Blood culture .....

☐ Culture positive ☐Yes ☐No ☐Unknown

If yes, which ☐Bacterial ☐Fungal ☐Viral

☐ Pathogen identified .....

☐ Urine culture .....

☐ Culture positive ☐Yes ☐No ☐Unknown

If yes, which ☐Bacterial ☐Fungal ☐Viral

☐ Pathogen identified .....

☐ Sputum culture .....

☐ Culture positive ☐Yes ☐No ☐Unknown

If yes, which ☐Bacterial ☐Fungal ☐Viral

☐ Pathogen identified .....

☐ Synovial culture .....

☐ Culture positive ☐Yes ☐No ☐Unknown

If yes, which ☐Bacterial ☐Fungal ☐Viral

☐ Pathogen identified .....

☐ Cerebrospinal fluid culture .....

☐ Culture positive ☐Yes ☐No ☐Unknown

If yes, which ☐Bacterial ☐Fungal ☐Viral

☐ Pathogen identified .....

☐ Tissue culture .....

If yes, specify ☐ Brain ☐ Lung ☐ Liver ☐Kidney ☐Skin ☐Bone ☐Other

☐ Culture positive ☐Yes ☐No ☐Unknown

If yes, which ☐Bacterial ☐Fungal ☐Viral

☐ Pathogen identified .....

☐ Catheter Tip/Line .....

☐ Culture positive ☐Yes ☐No ☐Unknown

If yes, which ☐Bacterial ☐Fungal ☐Viral

☐ Pathogen identified .....

☐ PPD placement ☐Yes ☐No ☐Unknown

If yes, PPD positive ☐Yes ☐No ☐Unknown

☐ Parasitic evaluation (ova, et.c) .....

☐ X-ray ☐Yes ☐No ☐Unknown

.....

☐ MRI ☐Yes ☐No ☐Unknown

.....

☐ CT scan ☐Yes ☐No ☐Unknown

.....

☐ Bone scan ☐Yes ☐No ☐Unknown

.....

☐ Other .....

☐ Rapid test .....

☐ Serum titres .....

☐ Hospital discharge report .....

☐ Other consult report .....

☐ Provide final diagnosis and treatment, if available (please specify):

.....

☐ Outcome and resolution date .....

TREATMENT

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

If yes, reason for ICU admission: .....

Overall length of hospital stay ☐ < 1 day ☐ > 1 day ☐ < 7 days ☐ > 7 days

.....

☐ In-hospital antibiotics	☐Yes	☐No	☐Unknown
If yes, route of administration	☐ IV	☐ Oral	☐Both oral and IV
☐ Other in-hospital treatment			
☐ Antivirals	☐Yes	☐No	☐Unknown
If yes, route of administration	☐ IV	☐ Oral	
☐ Antifungals	☐Yes	☐No	☐Unknown
If yes, route of administration	☐ IV	☐ Oral	
☐ Surgery	☐Yes	☐No	☐Unknown
☐ Hyperbaric oxygen	☐Yes	☐No	☐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 .....
- ☐ 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 .....

Please give any additional information or comments you consider relevant and have not been covered by the questionnaire:

.....

.....

.....

.....

.....

REPORTER INFORMATION

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

Name and title:.....

Affiliation:.....

Address:.....

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

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

Signature: .....

Denosumab – Osteonecrosis of the jaw questionnaire v1.0

- Supplement to the (S)AE Form -

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

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

PATIENT INFORMATION:

Age: .....

Gender: ☐M ☐F Pregnant: ☐Y ☐ N

Height ..... cm/ ..... in Weight ..... kg/ ..... lbs

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

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

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 subcutaneously (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 .....

ADVERSE EVENT DATA

Event reported term:.....

Event onset date (dd/mm/yyyy):.....

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 ☐Yes ☐No ☐Unknown

Please describe .....

Date exposed bone was first visualized/probed .....

Exposed bone or probed bone that has persisted for more than eight weeks:

☐Yes ☐No ☐Unknown .....

Prior history of radiation therapy lo jaw ☐Yes ☐No ☐Unknown

Prior history of metastatic disease to jaw: ☐Yes ☐No ☐Unknown

Describe: .....

Please describe location(s):

☐ Right maxilla, teeth and lateral jaw

☐ Left maxilla, teeth and lateral jaw

☐ Right maxilla, medial jaw

☐ Right mandible teeth and lateral jaw

☐ Left mandible teeth and lateral jaw

☐ Right mandible, medial jaw

☐ Maxilla hard palate

☐ Other (specify).....

ORAL FINDINGS

Evidence of infection: ☐Yes ☐No ☐Unknown

Please describe .....

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

Complete coverage of involved area(s) by mucosa: ☐Yes ☐No ☐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 (e.g., infection, pain, inflammation):

.....

Please describe the clinical signs/symptoms/location:

.....

.....

.....

.....

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

Dental/oral surgery/stomatology consultations ☐Yes ☐No ☐Unknown

If yes, please give date of examination .....

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

.....

TREATMENT

Antibiotics ☐Yes ☐No ☐Unknown

If yes, agent(s)/route/dose .....

Start date .....

Stop date .....

Please describe outcomes of treatment .....

Oral rinses ☐Yes ☐No ☐Unknown

If yes, agent(s)/dose .....

Please describe outcomes of treatment .....

Oral surgery ☐Yes ☐No ☐Unknown

If yes, type of surgery .....

Start date .....

Stop date .....

Please describe outcomes of treatment .....

Hospitalizations ☐Yes ☐No ☐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 ☐Yes ☐No ☐Unknown .....

Dental extraction recently ☐Yes ☐No ☐Unknown

If yes, date of procedure .....

Dental surgery recently ☐Yes ☐No ☐Unknown

If yes, date of procedure .....

Periodontal disease including gingival bleeding, calculus, etc. ☐Yes ☐No ☐Unknown

Start date .....

Stop date .....

Draining fistula in affected area ☐Yes ☐No ☐Unknown

Start date .....

Stop date .....

Dental abscess in affected area ☐Yes ☐No ☐Unknown

Start date .....

Stop date .....

Osteomyelitis in affected area ☐Yes ☐No ☐Unknown

Start date .....

Stop date .....

Root-canal treatment near affected area ☐Yes ☐No ☐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 ☐Yes ☐No ☐Unknown

History of dentures / dental appliance / implant ☐Yes ☐No ☐Unknown

If yes, please specify ☐ Upper ☐ Lower

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

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

PO bisphosphonate ☐Yes ☐No ☐Unknown

If yes, agent(s)/dose .....

Start date .....

Stop date .....

IV bisphosphonate ☐Yes ☐No ☐Unknown

If yes, agent(s)/dose .....

Start date .....

Stop date .....

Glucocorticoid use within the past 12 months ☐Yes ☐No ☐Unknown

If yes, agent(s)/dose .....

Start date .....

Stop date .....

Immunosuppressant use within the past 12 months ☐Yes ☐No ☐Unknown

If yes, agent(s)/dose .....

Start date .....

Stop date .....

Chemotherapy within the past 12 months ☐Yes ☐No ☐Unknown

If yes, agent(s)/dose .....

Start date .....

Stop date .....

Anti-angiogenic agents (e.g., bevacizumab) within the past 12 months ☐Yes ☐No ☐Unknown

If yes, agent(s)/dose .....

Start date .....

Stop date .....

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

Current smoker ☐Yes ☐No ☐Unknown

If yes, estimated number of pack-years .....

If past smoker, stop date .....

Alcohol consumption	☐Yes	☐No	☐Unknown
If yes, estimated drinks per week			
Diabetes	☐Yes	☐No	☐Unknown
If yes, type	☐Type 1		☐Type 2

PATIENT CARD STATUS

Received a patient card prior to the osteonecrosis of the jaw event?
☐Yes ☐No ☐Unknown

.....
.....

Please give any additional information or comments you consider relevant and have not been covered by the questionnaire:

.....
.....
.....
.....
.....

REPORTER INFORMATION

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

Name and title:.....

Affiliation:.....

Address:.....

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

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

Signature: .....

Denosumab – Atypical fractures (low energy, subtrochanteric/femoral shaft fractures) questionnaire v1.0

- Supplement to the (S)AE Form -

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

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

PATIENT INFORMATION:

Age: .....

Gender: ☐M ☐F Pregnant: ☐Y ☐ N

Height ..... cm/ ..... in Weight ..... kg/ ..... lbs

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

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

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 subcutaneously (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 .....

ADVERSE EVENT DATA

Reported event:.....

Event onset date (dd/mm/yyyy):.....

DIAGNOSIS (Check all that apply)

Location of fracture

☐ Femur neck

☐ Femur distal

☐ Femur midshaft

☐ Femur intertrochanter

☐ Femur subtrochanter

☐ Other location (specify): .....

Diagnostic imaging used to confirm fracture: ☐ X-ray ☐CT scan ☐MRI

Date of imaging at time of femur fracture (DD/MM/YYYY): .....

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

Was this a pathological fracture associated with bone tumour 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 breaking of the cortex:

☐ Yes ☐ No ☐ Not reported

Diffuse cortical thickening of the proximal femoral shaft

☐ Yes ☐ No ☐ Not reported

Type of trauma reported at time of fracture:

☐ No trauma

☐ Fall from standing height or less

☐ Fall on stairs, steps or curbs

☐ Fall from the height of stool, chair, first rung on a ladder or equivalent (about 20 inches)

☐ Minimal trauma other than a fall

☐ Fall from higher than the height of a stool, chair, first rung on a 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 site at rest

☐ Pain at site with weight bearing

☐ None

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

If yes:

Date of fracture union (DD/MM/YYYY): .....

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

Fracture union confirmed through imaging: ☐ Yes ☐ No ☐ Unknown

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

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

Please give any additional information or comments you consider relevant and have not been covered by the questionnaire:

REPORTER INFORMATION

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

Name and title:.....

Affiliation:.....

Address:.....

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

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

Signature: .....

Denosumab – Fracture healing questionnaire v1.0

- Supplement to the (S)AE Form -

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

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

PATIENT INFORMATION:

Age: .....

Gender: ☐M ☐F Pregnant: ☐Y ☐ N

Height ..... cm/ ..... in Weight ..... kg/ ..... lbs

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

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

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 subcutaneously (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 .....

ADVERSE EVENT DATA

Event reported term:.....

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

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

☐ Radius

☐ Rib

☐ Scapula

☐ Shoulder

☐ Sternum

☐ Ulna

☐ Wrist/carpal

☐ 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.)

.....

☐ Foot/tarsal/metatarsal/phalange

☐ Hip

☐ Patella

☐ Pelvis

☐ Tibia

☐ Fibula

☐ 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

TREATMENT (Please provide dates and indicate attachments if available):

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

☐ Casting .....

☐ Non-surgical reduction .....

☐ Surgery .....

☐ Revision surgery (2nd surgery) .....

☐Traction .....

☐ 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 of current corticosteroid use .....

☐ Prior fracture history .....

☐ Diabetes .....

Please give any additional information or comments you consider relevant and have not been covered by the questionnaire:

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.....

REPORTER INFORMATION

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

Name and title:.....

Affiliation:.....

Address:.....

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

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

Signature: .....

Denosumab – Malignancy questionnaire v1.0

- Supplement to the (S)AE Form -

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

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

PATIENT INFORMATION:

Age: .....

Gender: ☐M ☐F Pregnant: ☐Y ☐ N

Height ..... cm/ ..... in Weight ..... kg/ ..... lbs

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

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

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 subcutaneously (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 .....

ADVERSE EVENT DATA

Event reported term:.....

Event onset date (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): .....

Tumour stage, if known: .....

Primary site of malignancy: .....

TUMOUR STAGE:

Tumour Size (Check which one applies):

☐TX ☐T0 ☐Tis ☐T1 ☐T2 ☐T3 ☐T4

Tumour 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

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:) .....

Please give any additional information or comments you consider relevant and have not been covered by the questionnaire:

.....

.....

.....

.....

REPORTER INFORMATION:

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

Name and title:.....

Affiliation:.....

Address:.....

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

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

Signature: .....

Denosumab – Hypersensitivity questionnaire v1.0

- Supplement to the (S)AE Form -

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

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

PATIENT INFORMATION:

Age: .....

Gender: ☐M ☐F Pregnant: ☐Y ☐ N

Height ..... cm/ ..... in Weight ..... kg/ ..... lbs

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

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

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 subcutaneously (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 .....

☐ **Denosumab Antibody Testing Performed** (provide dates and results): .....

.....

ADVERSE EVENT DATA

Event reported term:.....

Event onset date (dd/mm/yyyy):.....

SIGNS AND SYMPTOMS (check all that apply)

☐ Anaphylaxis

☐ Angioneurotic oedema

☐ Colic

☐ Facial oedema

☐ Hypotension

☐ Laryngeal oedema

☐ Rash

☐ Shortness of breath

☐ Stridor

☐ Diarrhoea

☐ Pruritus

☐ Swelling

☐ Tachycardia

☐ Urticaria

☐ Wheezing

☐ Other (specify) .....

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

Diagnostic	**Results / Units**	**Reference range/ Units**	**Date (dd/mm/ yyyy)**	**Report attached Y/N**	**Diagnostic**	**Results/ Units**	**Reference range/ Units**	**Date (dd/mm /yyyy)**	**Report attached Y/N**
Results at BASELINE (prior to Teva's denosumab)					**Results at TIME OF EVENT**				
CBC with differential					CBC with differential				
WBC					WBC				
RBC					RBC				
Eosinophils					Eosinophils				
Hgb					Hgb				
Hct					Hct				
Platelets					Platelets				
Other					Other				
Albumin					Albumin				
Total protein					Total protein				
BUN					BUN				
Serum creatinine					Serum creatinine				
ALT					ALT				
AST					AST				
ALP					ALP				
Bilirubin					Bilirubin				
Calcium					Calcium				
K+					K+				
Na+					Na+				
Phosphorus					Phosphorus				
Mg++					Mg++				
Cl-					Cl-				
CrCl					CrCl				

TREATMENT

☐ ER corticosteroids

Route: ☐ IV ☐ 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 admissions/discharge report (please attach if available):

.....

.....

.....

.....

☐ Hypersensitivity event resolved ☐ Yes ☐ No ☐ Unknown

If yes, date of resolution (DD/MM/YYYY): .....

☐ Final diagnosis or etiology (incl. start date). Please send supporting documents for diagnosis

.....

☐ Other consult report (please indicate any attachments) .....

.....

.....

CONCOMITANT MEDICATIONS

☐ ACE inhibitors

☐ Alopurinol

☐ Cancer chemotherapy

☐ Dapsone

☐ IV contrast

☐ NSAIDs/acetylsalicylic acid

☐ Penicillamine

☐ Rifampicine

☐ Anticonvulsants (check which apply):

- ☐ Phenytoin
- ☐ Carbamazepine
- ☐ Phenobarbital

☐ Antibiotics (check which apply):

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

Please give any additional information or comments you consider relevant and have not been covered by the questionnaire:

.....

.....

.....

.....

REPORTER INFORMATION

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

Name and title:.....

Affiliation:.....

Address:.....

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

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

Signature: .....

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

Key messages of the additional risk minimisation measures:

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

The MAH shall ensure that in each Member State where denosumab is marketed, all healthcare professionals who are expected to prescribe denosumab and all patients/carers who are expected to use denosumab will have access to the Patient Card.

Patient Card:

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

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

- the risk of osteonecrosis of the jaw during treatment with denosumab;
- 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 denosumab and to contact their doctor and dentist if problems with the mouth or teeth occur during treatment.

The methods for dissemination and the target audience in each Member State will be agreed at the national level by the respective competent authority of the Member State.