EU RISK MANAGEMENT PLAN

Degevma (Denosumab)

(120 mg/1.7 mL solution for injection, vial)

RMP version to be assessed as part of this application	
RMP version number	1.1
Data lock point for this RMP	11 July 2024
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QPPV Details	
QPPV name:	Iva Novak
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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)	Degevma
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**: Prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with advanced malignancies involving bone.

	Treatment of adults and skeletally mature adolescents with giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity.
	Proposed (if applicable): Not applicable.
Dosage in the EEA	**Current**: Supplementation of at least 500 mg calcium and 400 IU vitamin D daily is required in all patients, unless hypercalcaemia is present. <u>Prevention of skeletal related events in adults with advanced malignancies involving bone</u> The recommended dose of denosumab is 120 mg administered as a single subcutaneous injection once every 4 weeks into the thigh, abdomen or upper arm. <u>Giant cell tumour of bone</u> The recommended dose of denosumab is 120 mg administered as a single subcutaneous injection once every 4 weeks into the thigh, abdomen or upper arm with additional 120 mg doses on days 8 and 15 of treatment of the first month of therapy.
	Proposed (if applicable): Not applicable.
Pharmaceutical form(s) and strengths	**Current**: 120 mg/1.7 mL solution for injection in single use vial (intended for subcutaneous use). Each vial contains 120 mg of denosumab in 1.7 mL of solution (70 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 Xgeva® (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 names PROLIA® and XGEVA® (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® and XGEVA® 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 (Xgeva®, 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

Study type	Important Nonclinical Safety Findings	Relevance to Human Usage
Reproductive toxicity	In single and repeated dose toxicity studies in cynomolgus monkeys, denosumab doses resulting in 2.7 to 15 times greater systemic exposure than the recommended human dose had no impact on male or female fertility (Xgeva® SmPC, 5.3). In a study of cynomolgus monkeys dosed with denosumab during the period equivalent to the first trimester of pregnancy, denosumab doses resulting in 9 times greater systemic exposure than the recommended human dose did not induce maternal toxicity or foetal harm during a period equivalent to the first trimester, although foetal lymph nodes were not examined (Xgeva® SmPC, 5.3). In another study of cynomolgus monkeys dosed with denosumab throughout pregnancy at systemic exposures 12-fold higher than the human dose, there were increased stillbirths and postnatal mortality; abnormal bone growth resulting in reduced bone strength, reduced haematopoiesis, and tooth malalignment; absence of peripheral lymph nodes; and decreased neonatal growth (Xgeva® SmPC, 5.3). There was no evidence of maternal harm prior to labour; adverse maternal effects occurred infrequently during labour. Maternal mammary gland development was normal (Xgeva® SmPC, 5.3).	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 (Xgeva® SmPC, 4.6). It is unknown whether denosumab is excreted in human milk. A risk to the newborns/infants cannot be excluded. Therefore, a decision must be made on whether to abstain from breast-feeding or to abstain from denosumab therapy (Xgeva® SmPC, 4.6) Use in pregnant and lactating women is not considered a safety concern in this RMP.

Study type	Important Nonclinical Safety Findings	Relevance to Human Usage
Developmental toxicity	Denosumab has been shown to be a potent inhibitor of bone resorption by inhibition of RANKL. Adolescent primates dosed with denosumab at 2.7 and 15 times (10 and 50 mg/kg dose) the clinical exposure had abnormal growth plates (Xgeva® SmPC, 5.3). In neonatal cynomolgus monkeys exposed in utero to denosumab at systemic exposures 12-fold higher than the human dose, there were increased stillbirths and 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 (Xgeva® SmPC, 5.3) In neonatal rats, inhibition of RANKL was associated with reduced bone growth, altered growth plates and impaired tooth eruption, and these changes were partially reversible upon cessation of RANKL inhibition (Xgeva® SmPC, 5.3).	The safety and efficacy of denosumab have not been established in paediatric patients (age < 18) other than skeletally mature adolescents (aged 12-17 years) with giant cell tumour of bone (Xgeva® SmPC, 4.2). Treatment with denosumab may impair bone growth in children with open growth plates and may inhibit eruption of dentition (Xgeva® SmPC, 5.3). 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 (Xgeva® SmPC, 4.6).

Part II: Module SIII - Clinical Trial Exposure

Teva's Denosumab (TVB 009) was developed as a biosimilar to Amgen's denosumab with an adequate biosimilar clinical development program. 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 Teva's denosumab, TVB-009X (DEGEVMA), 120 mg/1.7 mL solution for injection in a single-use vial, which was developed as a biosimilar to the reference product Xgeva®.

The tailored clinical development program comprised of two studies:

- 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-009) was developed as a biosimilar (application under Article 10(4) of Directive 2001/83/EC) to Xgeva® (Amgen Europe B.V.), a tailored clinical program was justified.

The clinical development program for TVB-009 drug product has been designed to demonstrate similarity of TVB-009P to PROLIA with regard to pharmacokinetic (PK), pharmacodynamic (PD), efficacy, safety, and immunogenicity.

The *in-vitro* comparison of PROLIA® and XGEVA® showed essential similarity in terms of composition. It can be concluded that denosumab exerts its pharmacodynamic activity via the same mechanism of action for all indications approved for PROLIA® and XGEVA®.

As a part of the clinical development program, two studies were 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). The safety and efficacy profile of Teva's denosumab (TVB-009P) was shown to be similar to the Amgen's Prolia.

The scientific justification for the extrapolation from clinical data in one of the approved indications (postmenopausal osteoporosis) of PROLIA® to the indications of XGEVA® that were not specifically studied in the clinical development program for TVB 009, is provided below.

A structural and functional assessment for biosimilarity was conducted for TVB-009 versus either PROLIA® or XGEVA® and demonstrated that TVB-009, i.e. both the TVB-009 prefilled syringe (TVB-009P) and TVB-009 vial (TVB-009X) were biosimilar to PROLIA® and XGEVA®. The composition for TVB-009 drug products is the same as the drug substance; the formulations of TVB-009P and TVB-009X differ only in the denosumab concentration of 60 mg/mL and 70 mg/mL, respectively. Similarity results demonstrated that TVB-009P and TVB-009X behave as expected analytically and functionally and that extrapolation can be supported with these results. To conclude, the structural and functional results indicate that TVB-009 is

biosimilar to PROLIA® and/or XGEVA®. Additional information is available in CTD 2.5 Clinical Overview, Appendix A.

The mechanism of action is deemed to be essentially similar for the studied indication of PROLIA® (i.e., postmenopausal osteoporosis) and all indications of XGEVA®.

Teva demonstrated PK similarity of TVB-009 and denosumab by comparing single administrations of TVB-009P and PROLIA® in healthy volunteers. Considering the compositions of the formulations, the PK of denosumab, and the results of analytical comparisons Teva concluded that pharmacokinetic similarity of TVB-009P and PROLIA® can be extrapolated to TVB-009X and XGEVA®.

Denosumab displayed dose-proportional PK in the dose range of 60 mg and 120 mg. The conclusion of PK/pharmacodynamic (PD) assessments in the pivotal PK/PD trial TVB009-BE-10157 and from sparse sampling in trial TVB009-IMB-30085 can therefore be extrapolated to the indications of XGEVA® as well.

The immunogenicity of TVB-009P was evaluated in healthy adult volunteers and in patients with postmenopausal osteoporosis. No immunogenicity of TVB-009 was observed in healthy participants and the incidence of anti-drug antibodies (ADA) in postmenopausal osteoporosis after TVB 009P administration was comparable between TVB-009P and PROLIA®. An immune response in cancer patients is less likely to appear due to an impaired immune system in these patients.

The adverse event profiles of PROLIA® and XGEVA® differ, due to the underlying life-threatening diseases for the XGEVA® indications. However, according to information in PROLIA SmPC, toxicity associated with denosumab may be similar for PROLIA® (60 mg) and XGEVA® (120 mg) and it can be expected that toxicity of TVB-009X is similar to XGEVA in the respective cancer patient populations (PROLIA® SmPC 2023).

Therefore, Teva considers that study results and conclusion obtained for the indication of postmenopausal osteoporosis can be extrapolated to the indications of XGEVA® as well.

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® and Xgeva® SmPC, 4.3).	No	Hypocalcaemia is a contraindication for denosumab therapy (Prolia® and Xgeva® SmPC, 4.3). Hypocalcaemia must be corrected before initiating therapy (Prolia® and Xgeva® SmPC, 4.4). Patients receiving denosumab must be adequately supplemented with calcium and vitamin D (Prolia® and Xgeva® SmPC, 4.2).
Known hypersensitivity to any components of the investigational medicinal product or to calcium or vitamin D	Contraindication for denosumab use (Prolia® and Xgeva® SmPC, 4.3).	No	Hypersensitivity to the active substance or to any of the excipients is a contraindication for denosumab therapy (Prolia® and Xgeva® SmPC 4.3).
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® and Xgeva® 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® and Xgeva® SmPC, 4.6). A decision on whether to abstain from breast-feeding or to abstain from therapy with denosumab should be made (Prolia® and Xgeva® 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 in patients receiving denosumab (Prolia® and Xgeva® 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 (Prolia® and Xgeva® SmPC, 4.4). Pre-existing condition or risk factors may confound the study results.	No	In line with the innovator's (Xgeva®, Amgen) approach, Osteonecrosis of the jaw is considered as an important identified risk in Teva's denosumab 120 mg/1.7 mL vial 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 (Xgeva®, Amgen) approach, Cardiovascular events are considered as an important potential risk in Teva's denosumab 120 mg/1.7 mL vial 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 (Xgeva®, Amgen) approach, Malignancy is considered as an important potential risk in Teva's denosumab 120 mg/1.7 mL vial 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 (Xgeva®, Amgen) approach, Infections are not considered as a safety concern in Teva's denosumab 120 mg/1.7 mL vial 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 (Xgeva®, Amgen) approach, Infections are not considered as a safety concern in Teva's denosumab 120 mg/1.7 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 dose and schedule of up to 120 mg monthly) (Xgeva® SmPC).	No	In line with innovator's (Xgeva®, Amgen) approach, mentioned metabolic or bone diseases are not considered as safety concerns in Teva's denosumab 120 mg/1.7 mL vial RMP.
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 (Xgeva®, Amgen) approach, vertebral fractures are not considered as a safety concern in Teva's denosumab 120 mg/1.7 mL vial RMP.

History and/or presence of hip fracture or atypical femur fracture	Atypical femoral fractures have been reported in patients receiving denosumab (Prolia® and Xgeva® 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® and Xgeva® SmPC, 4.4). Pre-existing conditions may confound study results.	No	In line with the innovator's (Xgeva®, Amgen) approach, Atypical femoral fracture is considered as an important identified risk in Teva's denosumab 120 mg/1.7 mL vial RMP.
Previous bisphosphonate treatment	Bisphosphonates 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.	Yes	In line with the innovator's (Xgeva®, Amgen) approach, denosumab use in patients with prior intravenous bisphosphonate treatment is considered as missing information in Teva's denosumab 120 mg/1.7 mL vial RMP.

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. Regular monitoring of calcium is especially important in these patients (Prolia® and Xgeva® SmPC, 4.4). No dose adjustment is required in patients with renal impairment (Prolia® and Xgeva®, 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. However, these types of adverse reactions could be detected during the more extensive clinical development and post-marketing experience of the reference drug. The established safety profile of the originator is also applicable for the biosimilar.

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® and Xgeva® SmPC, 4.6). According to the Prolia® and Xgeva® 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® and Xgeva® 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® and Xgeva® 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><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>Race group</td><td colspan="6"></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>Ethnicity</td><td colspan="6"></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>
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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 Xgeva® (Amgen) SmPC, section 4.2, the safety and efficacy of denosumab have not been established in paediatric patients (age < 18) other than skeletally mature adolescents (aged 12-17 years) with giant cell tumour of bone and denosumab is not recommended in paediatric patients other than skeletally mature adolescents with giant cell tumour of bone. Further, clinically significant hypercalcaemia after treatment discontinuation has been reported in the post-marketing setting for Xgeva® in paediatric patients (Xgeva® SmPC, section 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 Xgeva® SmPC, section 4.2, no dose adjustment is required in elderly (≥ 65 years) patients.</td></tr>
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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-009X, 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-009X was developed as a biosimilar to the reference product, Xgeva® (Amgen). The safety concerns for the biosimilar are expected to be the same as those for Xgeva®. 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 Xgeva® (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 v1.0 is in line with the reference product's (Xgeva®, Amgen) RMP v36.0, dated 11 December 2020, and published on 04 September 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: 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 randomized, controlled, phase 3 clinical studies of the originator (Xgeva®, Amgen) and further supported by postmarketing reports.
Characterisation of the risk	Frequency: 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 Xgeva® SmPC, osteonecrosis of the jaw has been reported commonly in patients receiving denosumab (Xgeva® SmPC, 4.4 and 4.8). Severity and reversibility of risk 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. Long-term outcomes and impact on the quality of life 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; Xgeva® 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). Good oral hygiene practices should be maintained during treatment with denosumab and dental health should be monitored (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 (SmPC, 4.4). In patients who develop ONJ during treatment with denosumab, a temporary interruption of treatment should be considered 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 based on the relative frequency observed in clinical trials and with the observations that most ONJ events appear to be moderate to severe in severity and resolve without requiring extensive surgical treatment..

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; Xgeva® SmPC, 4.4).
Evidence source(s) and strength of evidence	This risk was identified in randomized, controlled, phase 3 clinical studies and in open-label, phase 2 clinical studies of the originator (Xgeva®, Amgen). This risk was further supported by Xgeva® postmarketing reports.
Characterisation of the risk	<u>Frequency</u>: There were no reports of atypical femoral fracture during the Study 30085 (or 10157). According to Xgeva® (Amgen) SmPC, atypical femoral fractures have been reported uncommonly in patients receiving denosumab (Prolia® SmPC, 4.8). <u>Severity and reversibility of risk</u> According to Xgeva® (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 (Xgeva® SmPC, 4.4). It is unknown if the pathophysiological mechanism(s) contributing to the development of AFF are reversible after treatment is discontinued. <u>Long-term outcomes and impact on the quality of life</u> 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; Xgeva® 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 frequency of AFF in patients treated with denosumab, the size of the indicated populations, and usage patterns of denosumab in clinical practice, no significant additional public health impact is expected.

Important Identified Risk: Hypercalcaemia Several Months After the Last Dose in Patients With Giant Cell Tumour of Bone and in Patients with Growing Skeletons	
Potential mechanisms	The mechanism(s) of hypercalcemia several months after the last dose of denosumab in patients with giant cell tumour of bone (GCTB) and in patients with a growing skeleton are not well characterized, but may be a consequence of the following, alone, or in combination: Denosumab treatment and resultant RANK/RANKL pathway inhibition in adults with giant-cell containing lesions such as GCTB leads to histopathologic evidence of a dramatic decrease in osteoclast-like giant cells which is complemented by woven bone formation and calcification within the tumours and even at sites of distant metastases (Ghermandi et al, 2016; Yamagishi et al, 2016). It is possible this calcium could serve as a depot that is mobilized with reactivation of tumor-associated, RANKL driven giant cell mediated osteolysis following cessation of denosumab. • 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 the skeleton either near the growth plates (as can be the case with the young adult and adolescent patients) or from the giant cell tumours themselves that have partially ossified in the cases of the adult patients with tumour recurrence via an autocrine/paracrine mechanism (Cowan et al, 2011). • The magnitude of the resorptive response following treatment withdrawal in the patients with GCTB and in those with an immature skeleton could be dictated by the normal high rate of bone turnover within the GCTB lesion or in the growing skeletons of young patients.

	• The response of the osteoclast lineage to loss of inhibition of osteoclastogenesis may be intrinsically more robust in young individuals or may be affected by intratumor signaling pathways (eg, parathyroid hormone-related protein) in GCTB.
Evidence source(s) and strength of evidence	This risk was identified in phase 2 clinical trials of adolescent and adult patients with GCTB, performed by innovator, and in postmarketing reports of paediatric patients using denosumab for unauthorized indications.
Characterisation of the risk	Frequency: Patients with bone disease (except with postmenopausal osteoporosis), as well as paediatric patients, were excluded from TVB-009 clinical development program. According to Xgeva® (Amgen) SmPC, hypercalcaemia following treatment discontinuation in patients with giant cell tumour of bone is an adverse reaction with uncommon frequency (Xgeva® SmPC, 4.8). Severity and reversibility of risk According to Xgeva® (Amgen) SmPC, clinically significant hypercalcaemia requiring hospitalisation and complicated by acute renal injury has been reported in denosumab-treated patients with giant cell tumour of bone weeks to months following treatment discontinuation; clinically significant hypercalcaemia has also been reported in patients with growing skeletons weeks to months following treatment discontinuation (Xgeva® SmPC, 4.4). Long-term outcomes and impact on the quality of life Paediatric patients may present with severe hypercalcemia requiring hospitalization. Patients who experience hypercalcemia may develop complications such as acute renal injury.
Risk factors and risk groups	Patients with GCTB and young patients with growing skeletons following discontinuation of denosumab. In general, the most common cause of hypercalcemia in humans is hyperparathyroidism, particularly among women and individuals aged 65 years or older (Tonono et al, 2022). Hyperthyroidism and rhabdomyolysis associated with renal failure also increase the risk of hypercalcemia, as does the ingestion of large of amounts of calcium through dairy products or more recently liberal use of calcium supplements (Motlaghzadeh et al, 2021).
Preventability	No preventive measures are known. After treatment is discontinued, patients should be monitored for signs and symptoms of hypercalcaemia, periodic assessment of serum calcium should be considered and the patient's calcium and vitamin D supplementation requirements should be re-evaluated (SmPC section 4.4). Denosumab is not recommended in patients with growing skeletons (SmPC section 4.2 and 4.4).
Impact on the risk-benefit balance of the product	The risk of hypercalcemia events several months after the last dose in patients with GCTB and in patients with growing skeletons has been considered in the product benefit-risk assessment. In light of the product labeling that has been proposed to minimize 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 hypercalcemia several months after the last dose in patients with GCTB occurs uncommonly and GCTB is a rare tumour. Off-label use of denosumab in paediatric patients appears to be limited to rare conditions for which there is significant unmet medical need.

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	The risk of cardiovascular events is a theoretical concern based on the epidemiological association between OPG levels and cardiovascular disease. Clinical data have not substantiated a cause-and-effect relationship between OPG and atherosclerotic processes nor between denosumab or inhibition of RANKL and undesirable cardiovascular outcomes.
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.

	Severity and reversibility of risk 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. Long-term outcomes and impact on the quality of life 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 cyclooxygenase-2 (COX-2) inhibitors (Murphy and Dargie, 2007; Smith et al, 2004).
Preventability	Based on clinical data to date, denosumab has not been associated with an increased incidence or severity of cardiovascular adverse effects; therefore, no preventive measures are defined. Patients at risk of cardiovascular events should be managed according to usual standards of care.
Impact on the risk-benefit balance of the product	The potential risk of cardiovascular events has been considered in in the product benefit-risk risk assessment, and the overall benefit-risk balance is considered to be positive.
Potential public health impact of safety concern	Significant public health impact on cardiovascular disease severity or incidence is not expected based on the information from denosumab clinical studies in the advanced cancer and postmenopausal osteoporosis/hormone ablation therapy settings.

Important Potential Risk: Malignancy	
Potential mechanisms	The risk of malignancy is a theoretical concern that RANKL inhibition may lead to an increased risk for a new primary malignancy (NPM) by impairing immune surveillance mechanisms.
Evidence source(s) and strength of evidence	Imbalance is observed in the NPM events between the zoledronic acid and Xgeva® treatment groups in the pivotal clinical studies for originator (Xgeva®, Amgen). The results of originator's postmarketing retrospective cohort study, showed NPM incidence rates for Xgeva® were generally lower than those for zoledronic acid in unadjusted analyses, suggesting no obvious excess risk associated with denosumab.
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. Long-term outcomes and impact on the quality of life Malignancy is typically disabling and may require surgery, radiation, and/or chemotherapy.
Risk factors and risk groups	General factors for increasing risk of NPM include advancing age, diet, cigarette smoking, excessive ethanol consumption, and numerous environmental toxins. In addition, advanced cancer populations are at increased risk for NPM because of their existing malignancy, possible genetic predisposition, and exposure to chemotherapy and radiation treatment (Anand et al, 2008; WHO, 2010).
Preventability	Second malignant neoplasms have become increasingly recognized and current recommendations include vigilance for these cancers in adult cancer survivors. SmPC recommends that patients should be monitored for radiological signs of malignancy, new radiolucency or osteolysis (SmPC, 4.4).
Impact on the risk-benefit balance of the product	The risk of malignancy events has been considered in the product benefit-risk assessment. In light of the product labeling that has been

	proposed to minimize 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 based on the information from studies in the postmenopausal osteoporosis/hormone ablation therapy and advanced cancer settings.

Important Potential Risk: Delay in diagnosis of primary malignancy in giant cell tumour of bone	
Potential mechanisms	Due to well described sampling error at the time of GCTB diagnosis, primary malignancy in giant cell tumour of bone (PMGCTB) may be missed and benign GCTB may be presumed. Based on the mechanism of action and pathology of GCTB, denosumab is only expected to treat benign GCTB. However, there was a theoretical concern that treatment of an undiagnosed PMGCTB with denosumab could delay the diagnosis of PMGCTB.
Evidence source(s) and strength of evidence	The risk of delay in diagnosis of PMGCTB is a theoretical concern based on the difficulties in diagnosing PMGCTB in originator's (Xgeva®, Amgen) study.
Characterisation of the risk	Frequency: Patients with bone disease (other than postmenopausal osteoporosis) were excluded from TVB-009 clinical development program. According to Xgeva® (Amgen) SmPC, malignancy in giant cell tumour of bone or progression to metastatic disease is a known risk in patients with giant cell tumour of bone (Xgeva® SmPC, 4.4). Severity and reversibility of risk Not applicable. Long-term outcomes and impact on the quality of life No data on long-term outcomes are available. Malignancy is typically disabling and may require surgery, chemotherapy, and/or radiotherapy.
Risk factors and risk groups	Patients with GCTB are known to be at risk for PMGCTB.
Preventability	No preventive measures are known. SmPC recommends that patients should be monitored for radiological signs of malignancy, new radiolucency or osteolysis (SmPC, 4.4).
Impact on the risk-benefit balance of the product	The risk of delay in diagnosis of PMGCTB events has been considered in the product benefit-risk assessment. In light of the product labeling that has been proposed to minimize this risk, the overall benefit-risk balance is considered to be positive.
Potential public health impact of safety concern	Given that GCTB is very rare condition, no impact on public health is expected.

Important Potential Risk: Hypercalcaemia Several Months After the Last Dose in Patients Other than Those with Giant Cell Tumour of Bone or Growing Skeletons	
Potential mechanisms	The pathogenesis of hypercalcemia several months after the last dose in patients other than those with GCTB or growing skeletons may be a consequence of the transient increase in bone turnover activity. Upon cessation of denosumab, the disinhibition of RAN KL allows for terminal differentiation and activation of osteoclasts, which were suppressed during treatment. In patients with underlying causes for calcium dyscrasias (ie, subclinical hyperparathyroidism), denosumab discontinuation, with its transient increase in bone remodeling and accompanying release of bone mineral, could theoretically be associated with transient hypercalcemia in susceptible individuals if the normal homeostatic mechanism regulating serum calcium are not appropriately maintained.
Evidence source(s) and strength of evidence	Hypercalcemia several months after the last dose in patients other than those with GCTB or growing skeletons is a theoretical concern based on the identified risk in other specific populations, GCTB, and paediatric populations.
Characterisation of the risk	Frequency: Patients with malignancies were excluded from TVB-009P clinical development program. Severity and reversibility of risk Not known. Long-term outcomes and impact on the quality of life No data on long-term outcomes are available. Patients may present with severe hypercalcemia requiring hospitalization. Patients who experience hypercalcemia may develop complications such as acute renal injury.
Risk factors and risk groups	Patients other than those with GCTB or growing skeletons following cessation of denosumab.
Preventability	No preventive measures are known.
Impact on the risk-benefit balance of the product	The risk of hypercalcemia events following treatment discontinuation in patients other than those with GCTB or growing skeletons has been incorporated in the product benefit-risk assessment, and the overall benefit-risk balance remains positive.
Potential public health impact of safety concern	No significant public health impact is expected as the potential events remain infrequent.

Table 13: Presentation of the Missing Information

Missing information: Patients with prior intravenous bisphosphonate treatment	
Evidence source	In the originator's (Xgeva®, Amgen) study, the incidence of ONJ in patients with prior intravenous bisphosphonate use was similar to that of patients who only received denosumab. No notable association was evident between ONJ and prior use of bisphosphonates.

Missing information: Patients with prior intravenous bisphosphonate treatment	
	Patients with prior bisphosphonate treatment were excluded from TVB-009P clinical development program.
Population in need of further characterisation	There is information from studies in patients with cancer showing that there is no increased risk of serious complications caused by bone metastases in patients who received Xgeva® following treatment with bisphosphonates. However, more information is needed. According to Xgeva® SmPC, some of the risk factors which should be considered when evaluating a patient's risk of developing ONJ include potency of the medicinal product that inhibits bone resorption (higher risk for highly potent compounds), route of administration (higher risk for parenteral administration) and cumulative dose of bone resorption therapy (Xgeva® SmPC, 4.4).

Missing information: Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumour of bone	
Evidence source	The overall safety profile of denosumab in the originator's (Xgeva®, Amgen) study was similar to the safety profile of Xgeva® observed in the treatment of subjects with advanced cancer and bone metastases. Patients with bone disease (other than postmenopausal osteoporosis), as well as paediatric patients, were excluded from TVB-009P clinical development program.
Population in need of further characterisation	Information on safety with long-term treatment and with long-term follow-up in adults or adolescents with GCTB will be monitored by routine pharmacovigilance activities.

Missing information: Off-label use in patients with giant cell tumor of bone that is resectable where resection is unlikely to result in severe morbidity	
Evidence source	No formal studies have been completed to determine originator's (Xgeva®, Amgen) effect on off-label use in patients with GCTB that is resectable where resection is unlikely to result in severe morbidity. Patients with bone disease (other than postmenopausal osteoporosis) were excluded from TVB-009P clinical development program.
Population in need of further characterisation	Information is not available on safety in patients with GCTB that is resectable where resection is unlikely to result in severe morbidity.

Part II: Module SVIII - Summary of the Safety Concerns

Table 14: Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	• Osteonecrosis of the jaw • Atypical femoral fracture • Hypercalcaemia several months after the last dose in patients with giant cell tumour of bone and in patients with growing skeletons
Important potential risks	• Cardiovascular events • Malignancy • Delay in diagnosis of primary malignancy in giant cell tumour of bone • Hypercalcaemia several months after the last dose in patients other than those with giant cell tumour of bone or growing skeletons
Missing information	• Patients with prior intravenous bisphosphonate treatment • Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumour of bone • Off-label use in patients with giant cell tumour of bone that is resectable where resection is unlikely to result in severe morbidity

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 15: List of Questionnaires

Safety concern for which the questionnaire is used	Purpose	Trigger events*
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

*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 16: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation measures
IMPORTANT IDENTIFIED RISKS	
Osteonecrosis of the jaw	**Routine risk communication:** Risk is addressed in SmPC sections 4.3, 4.4and 4.8. 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: Medicinal product subject to restricted medical prescription. The administration of the denosumab 120 mg/1.7 mL vial should only be performed by a healthcare professional.
Atypical femoral fracture	**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:** 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: Medicinal product subject to restricted medical prescription. The administration of the denosumab 120 mg/1.7 mL vial should only be performed by a healthcare professional.

Safety concern	Routine risk minimisation measures
Hypercalcemia several months after the last dose in patients with giant cell tumour of bone and in patients with growing skeletons	**Routine risk communication:** Risk is addressed in SmPC sections 4.2, 4.4 and 4.8. Described in PL sections 2 and 4. **Routine risk minimisation measures recommending specific clinical measures to address the risk:** After treatment is discontinued, monitor patients for signs and symptoms of hypercalcaemia, consider periodic assessment of serum calcium and re-evaluate the patient's calcium and vitamin D supplementation requirements (SmPC section 4.4). Denosumab is not recommended in patients with growing skeletons (SmPC section 4.2). **Other routine risk minimisation measures beyond the Product Information:** Legal status: Medicinal product subject to restricted medical prescription. The administration of the denosumab 120 mg/1.7 mL vial should only be performed by a healthcare professional.
IMPORTANT POTENTIAL RISKS	
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: Medicinal product subject to restricted medical prescription. The administration of the denosumab 120 mg/1.7 mL vial should only be performed by a healthcare professional.
Malignancy	**Routine risk communication:** Risk is addressed in SmPC sections 4.4 and 4.8. Described in PL section 4. **Routine risk minimisation measures recommending specific clinical measures to address the risk:** Patients should be monitored for radiological signs of malignancy, new radiolucency or osteolysis (SmPC section 4.4). **Other routine risk minimisation measures beyond the Product Information:** Legal status: Medicinal product subject to restricted medical prescription. The administration of the denosumab 120 mg/1.7 mL vial should only be performed by a healthcare professional.

Safety concern	Routine risk minimisation measures
Delay in diagnosis of primary malignancy in giant cell tumour of bone	**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: Medicinal product subject to restricted medical prescription. The administration of the denosumab 120 mg/1.7 mL vial should only be performed by a healthcare professional.
Hypercalcemia several months after the last dose in patients other than those with giant cell tumour of bone or growing skeletons	**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: Medicinal product subject to restricted medical prescription. The administration of the denosumab 120 mg/1.7 mL vial should only be performed by a healthcare professional.
MISSING INFORMATION	
Patients with prior intravenous bisphosphonate treatment	**Routine risk communication:** Risk is addressed in SmPC sections 4.5 and 5.1. Described in PL section 2. **Routine risk minimisation measures recommending specific clinical measures to address the risk:** None. **Other routine risk minimisation measures beyond the Product Information:** Legal status: Medicinal product subject to restricted medical prescription. The administration of the denosumab 120 mg/1.7 mL vial should only be performed by a healthcare professional.

Safety concern	Routine risk minimisation measures
Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumour of bone	**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: Medicinal product subject to restricted medical prescription. The administration of the denosumab 120 mg/1.7 mL vial should only be performed by a healthcare professional.
Off-label use in patients with giant cell tumour of bone that is resectable where resection is unlikely to result in severe morbidity	**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: Medicinal product subject to restricted medical prescription. The administration of the denosumab 120 mg/1.7 mL vial should only be performed by a healthcare professional.

V.2. Additional Risk Minimisation Measures

Table 17: 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 cancer-related conditions, including: • the risk of osteonecrosis of the jaw during treatment with denosumab; • to tell their doctor/nurse if they have any problems with their mouth or teeth before starting treatment; • to maintain good oral hygiene and receive routine dental check-ups during treatment; • to inform their doctor and tell their dentist that they are being treated with denosumab if they are under dental treatment or will undergo dental surgery; and • to contact their doctor and dentist immediately if they experience any problems with their mouth or teeth such as loose teeth, pain or swelling, non-healing of sores or discharge.

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

Safety concern	Risk minimisation measures	Pharmacovigilance activities
IMPORTANT IDENTIFIED RISKS		
Osteonecrosis of the jaw	**Routine risk minimisation measures:** SmPC sections 4.3, 4.4 and 4.8. PL sections 2 and 4. Medicinal product subject to restricted medical prescription. The administration of the denosumab 120 mg/1.7 mL vial should only be performed by a healthcare professional. **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
Atypical femoral fracture	**Routine risk minimisation measures:** SmPC sections 4.4 and 4.8. PL sections 2 and 4. Medicinal product subject to restricted medical prescription. The administration of the denosumab 120 mg/1.7 mL vial should only be performed by a healthcare professional. **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 several months after the last dose in patients with giant cell tumour of bone and in patients with growing skeletons	**Routine risk minimisation measures:** SmPC sections 4.2, 4.4 and 4.8. PL sections 2 and 4. Medicinal product subject to restricted medical prescription. The administration of the denosumab 120 mg/1.7 mL vial should only be performed by a healthcare professional. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
IMPORTANT POTENTIAL RISKS		
Cardiovascular events	**Routine risk minimisation measures:** Medicinal product subject to restricted medical prescription. The administration of the denosumab 120 mg/1.7 mL vial should only be performed by a healthcare professional. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Malignancy	**Routine risk minimisation measures:** SmPC sections 4.4 and 4.8. PL section 4. Medicinal product subject to restricted medical prescription. The administration of the denosumab 120 mg/1.7 mL vial should only be performed by a healthcare professional. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Delay in diagnosis of primary malignancy in giant cell tumor of bone	**Routine risk minimisation measures:** Medicinal product subject to restricted medical prescription. The administration of the denosumab 120 mg/1.7 mL vial should only be performed by a healthcare professional. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Hypercalcemia several months after the last dose in patients other than those with giant cell tumor of bone or growing skeletons	**Routine risk minimisation measures:** Medicinal product subject to restricted medical prescription. The administration of the denosumab 120 mg/1.7 mL vial should only be performed by a healthcare professional. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
MISSING INFORMATION		

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Patients with prior intravenous bisphosphonate treatment	**Routine risk minimisation measures:** SmPC sections 4.5 and 5.1 PL section 2. Medicinal product subject to restricted medical prescription. The administration of the denosumab 120 mg/1.7 mL vial should only be performed by a healthcare professional. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumour of bone	**Routine risk minimisation measures:** Medicinal product subject to restricted medical prescription. The administration of the denosumab 120 mg/1.7 mL vial should only be performed by a healthcare professional. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Off-label use in patients with giant cell tumour of bone that is resectable where resection is unlikely to result in severe morbidity	**Routine risk minimisation measures:** Medicinal product subject to restricted medical prescription. The administration of the denosumab 120 mg/1.7 mL vial should only be performed by a healthcare professional. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.

Part VI: Summary of the Risk Management Plan

Summary of Risk Management Plan for Degevma (Denosumab 120 mg/1.7 mL solution for injection, vial)

This is a summary of the risk management plan (RMP) for Degevma (Denosumab 120 mg/1.7 mL solution for injection, vial; herein after also referred to as Degevma). The RMP details important risks of Degevma, how these risks can be minimised, and how more information will be obtained about Degevma's risks and uncertainties (missing information).

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

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

I. The Medicine and What It is used for

Degevma (Denosumab 120 mg/1.7 mL solution for injection, vial) is authorised for the prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with advanced malignancies involving bone, as well as treatment of adults and skeletally mature adolescents with giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity (see SmPC for the full indication). It contains Denosumab 120 mg as the active substance and it is given by subcutaneous injection.

Further information about the evaluation of Degevma’s benefits can be found in Degevma’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 Degevma, together with measures to minimise such risks and the proposed studies for learning more about Degevma’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 Degevma, 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 Degevma 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 Degevma. 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 19: Summary of Safety Concerns

List of important risks and missing information	
Important identified risks	• Osteonecrosis of the jaw • Atypical femoral fracture • Hypercalcaemia several months after the last dose in patients with giant cell tumour of bone and in patients with growing skeletons
Important potential risks	• Cardiovascular events • Malignancy • Delay in diagnosis of primary malignancy in giant cell tumour of bone • Hypercalcemia several months after the last dose in patients other than those with giant cell tumour of bone or growing skeletons
Missing information	• Patients with prior intravenous bisphosphonate treatment • Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumour of bone • Off-label use in patients with giant cell tumour of bone that is resectable where resection is unlikely to result in severe morbidity

II.B Summary of Important Risks

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

Table 20: Summary of Pharmacovigilance Activities and Additional Risk Minimisation Activities by Safety Concern

Important identified risk: Osteonecrosis of the jaw	
Evidence for linking the risk to the medicine	This risk was identified in randomized, controlled, phase 3 clinical studies of the originator (Xgeva®, Amgen) and further supported by postmarketing reports.
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; Xgeva® Canadian Product Monograph, Warnings and Precautions section).
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.3, 4.4 and 4.8. PL sections 2 and 4. Medicinal product subject to restricted medical prescription. The administration of the denosumab 120 mg/1.7 mL vial should only be performed by a healthcare professional. Additional risk minimisation measures Patient card.
Important identified risk: Atypical Femoral Fracture	
Evidence for linking the risk to the medicine	This risk was identified in randomized, controlled, phase 3 clinical studies and in open-label, phase 2 clinical studies of the originator (Xgeva®, Amgen). This risk was further supported by Xgeva® postmarketing reports.
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; Xgeva® SmPC, 4.4).

Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.4 and 4.8. PL sections 2 and 4. Medicinal product subject to restricted medical prescription. The administration of the denosumab 120 mg/1.7 mL vial should only be performed by a healthcare professional. Additional risk minimisation measures None.
Important identified risk: Hypercalcemia several months after the last dose in patients with giant cell tumour of bone and in patients with growing skeletons	
Evidence for linking the risk to the medicine	This risk was identified in phase 2 clinical trials of adolescent and adult patients with GCTB, performed by innovator, and in postmarketing reports of paediatric patients using denosumab for unauthorized indications.
Risk factors and risk groups	Patients with GCTB and young patients with growing skeletons following discontinuation of denosumab. In general, the most common cause of hypercalcemia in humans is hyperparathyroidism, particularly among women and individuals aged 65 years or older (Tonono et al, 2022). Hyperthyroidism and rhabdomyolysis associated with renal failure also increase the risk of hypercalcemia, as does the ingestion of large of amounts of calcium through dairy products or more recently liberal use of calcium supplements (Motlaghzadeh et al, 2021).
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.2, 4.4 and 4.8. PL sections 2 and 4. Medicinal product subject to restricted medical prescription. The administration of the denosumab 120 mg/1.7 mL vial should only be performed by a healthcare professional. Additional risk minimisation measures None.
Important potential risk: Cardiovascular events	
Evidence for linking the risk to the medicine	The risk of cardiovascular events is a theoretical concern based on the epidemiological association between OPG levels and cardiovascular disease. Clinical data have not substantiated a cause-and-effect relationship between OPG and atherosclerotic processes nor between denosumab or inhibition of RANKL and undesirable cardiovascular outcomes.

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 cyclooxygenase-2 (COX-2) inhibitors (Murphy and Dargie , 2007; Smith et al, 2004).
Risk minimisation measures	Routine risk minimisation measures Medicinal product subject to restricted medical prescription. The administration of the denosumab 120 mg/1.7 mL vial should only be performed by a healthcare professional. Additional risk minimisation measures None.
Important potential risk: Malignancy	
Evidence for linking the risk to the medicine	Imbalance is observed in the NPM events between the zoledronic acid and Xgeva® treatment groups in the pivotal clinical studies for originator (Xgeva®, Amgen). The results of originator's postmarketing retrospective cohort study, showed NPM incidence rates for Xgeva® were generally lower than those for zoledronic acid in unadjusted analyses, suggesting no obvious excess risk associated with denosumab.
Risk factors and risk groups	General factors for increasing risk of NPM include advancing age, diet, cigarette smoking, excessive ethanol consumption, and numerous environmental toxins. In addition, advanced cancer populations are at increased risk for NPM 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 SmPC sections 4.4 and 4.8. PL section 4. Medicinal product subject to restricted medical prescription. The administration of the denosumab 120 mg/1.7 mL vial should only be performed by a healthcare professional. Additional risk minimisation measures None.
Important potential risk: Delay in diagnosis of primary malignancy in giant cell tumor of bone	
Evidence for linking the risk to the medicine	The risk of delay in diagnosis of PMGCTB is a theoretical concern based on the difficulties in diagnosing PMGCTB in originator's (Xgeva®, Amgen) study.
Risk factors and risk groups	Patients with GCTB are known to be at risk for PMGCTB.

Risk minimisation measures	Routine risk minimisation measures Medicinal product subject to restricted medical prescription. The administration of the denosumab 120 mg/1.7 mL vial should only be performed by a healthcare professional. Additional risk minimisation measures None.
Important potential risk: Hypercalcemia several months after the last dose in patients other than those with giant cell tumour of bone or growing skeletons	
Evidence for linking the risk to the medicine	Hypercalcemia several months after the last dose in patients other than those with GCTB or growing skeletons is a theoretical concern based on the identified risk in other specific populations, GCTB, and paediatric populations.
Risk factors and risk groups	Patients other than those with GCTB or growing skeletons following cessation of denosumab.
Risk minimisation measures	Routine risk minimisation measures Medicinal product subject to restricted medical prescription. The administration of the denosumab 120 mg/1.7 mL vial should only be performed by a healthcare professional. Additional risk minimisation measures None.
Missing information: Patients with prior intravenous bisphosphonate treatment	
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.5 and 5.1. PL section 2. Medicinal product subject to restricted medical prescription. The administration of the denosumab 120 mg/1.7 mL vial should only be performed by a healthcare professional. Additional risk minimisation measures None.
Missing information: Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumour of bone	
Risk minimisation measures	Routine risk minimisation measures Medicinal product subject to restricted medical prescription. The administration of the denosumab 120 mg/1.7 mL vial should only be performed by a healthcare professional. Additional risk minimisation measures None.

Missing information: Off-label use in patients with giant cell tumor of bone that is resectable where resection is unlikely to result in severe morbidity	
Risk minimisation measures	Routine risk minimisation measures Medicinal product subject to restricted medical prescription. The administration of the denosumab 120 mg/1.7 mL vial should only be performed by a healthcare professional. 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 Degevma.

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

There are no studies required for Degevma.

Part VII: Annexes

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Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Annex 3 – Protocols for proposed, ongoing and completed studies in the pharmacovigilance plan

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Annex 5 – Protocols for proposed and ongoing studies in RMP part IV

Annex 6 – Details of proposed additional risk minimisation activities (if applicable)

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Annex 4 – Specific Adverse Drug Reaction Follow-Up Forms

Follow-up forms

- Denosumab – Osteonecrosis of the jaw questionnaire v1.0
- Denosumab – Atypical fractures (low energy, subtrochanteric/femoral shaft fractures) questionnaire v1.0

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

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☐ 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: .....

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 cancer-related conditions, including:

- the risk of osteonecrosis of the jaw during treatment with denosumab;
- to tell their doctor/nurse if they have any problems with their mouth or teeth before starting treatment;
- to maintain good oral hygiene and receive routine dental check-ups during treatment;;
- to inform their doctor and tell their dentist that they are being treated with denosumab if they are under dental treatment or will undergo dental surgery;
- to contact their doctor and dentist immediately if they experience any problems with their mouth or teeth such as loose teeth, pain or swelling, nonhealing of sores, or discharge.

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.