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

RMP No.: L08/25

RMP version to be assessed as part of this application:

RMP version number:	1.0
Data lock point for this RMP:	23/09/2024
Date of final sign off:	13/03/2025

Rationale for submitting an updated RMP:

Not applicable

Summary of significant changes in this RMP:

Not applicable

Other RMP versions under evaluation:

RMP version number:	Not applicable
Submitted on:	Not applicable
Procedure number:	Not applicable

Details of the currently approved RMP:

RMP version number:	Not applicable
Approved within procedure:	Not applicable
Date of approval (opinion date):	Not applicable

Page of Authorisation

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

QPPV name: Ludmila FILIPOVÁ, MD

QPPV signature: The electronic signature is available on file.

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List of abbreviations

ADR	Adverse drug reaction
AFF	Atypical femoral fracture
AIDS	Acquired immune deficiency syndrome
AAOMS	American Association of Oral Maxillofacial Surgeons
ATC	Anatomical Therapeutic Chemical
AAC	Area above the curve
BCAT	Breast cancer adjuvant therapy
CKD	Chronic kidney disease
COX-2	Cyclooxygenase-2
CrCI	Creatinine clearance
CRPC	Castrate-resistant prostate cancer
CV	Cardiovascular
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ER	Emergency room
EU	European Union
GCTB	Giant cell tumor of bone
HALT	Hormone ablation therapy
HCM	Hypercalcemia of malignancy
HIV	Human immunodeficiency virus
IgG	Immunoglobulin G
INN	International Nonproprietary Name
iPTH	Intact parathyroid hormone
IV	Intravenous or intravenously
MAH	Marketing authorization holder
MM	Multiple myeloma
NPM	New primary malignancy
NSCLC	Stage IV untreated non-small cell lung carcinoma with or without bone metastasis

ONJ	Osteonecrosis of the jaw
OPG	Osteoprotegerin
PI	Product Information
PIL	Patient Information Leaflet
PMGCTB	Primary malignant giant cell tumor of bone
PMO	Postmenopausal osteoporosis
PSUR	Periodic safety update report
PTH	Parathyroid hormone
PY	Person-years of follow-up
Q4W	Every 4 weeks
QPPV	Qualified Person for Pharmacovigilance
RA	Rheumatoid arthritis
RANK	Receptor activator of nuclear factor kappa-B
RANKL	RANK ligand
RMP	Risk management plan
SC	Subcutaneous
SmPC	Summary of product characteristics
SRE	Skeletal-related event
ULN	Upper limit of normal
US	United States
ZA	Zoledronic acid

PART I: Product(s) overview

Active substance(s) (INN or common name)	Denosumab biosimilar
Pharmacotherapeutic group(s) (ATC code)	Drugs for treatment of bone diseases – Other drugs affecting bone structure and mineralisation (M05BX04)
Marketing authorisation applicant	Zentiva k.s.
Medicinal product(s) to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	ENWYLMA
Marketing authorisation procedure	Centralised (EMEA/H/C/0006376)
Brief description of the product	Chemical class Denosumab biosimilar, the active substance of ENWYLMA, is an immunoglobulin IgG2 isotype monoclonal antibody.
	Summary of mode of action Denosumab has high affinity and specificity for the soluble and cell membrane-bound forms of human receptor activator of nuclear factor kappa-B(RANK) ligand (RANKL), preventing the RANKL/RANK interaction from occurring and resulting in reduced osteoclast numbers and function, thereby decreasing bone resorption and cancer-induced bone destruction.
	Important information about its composition Denosumab is a human monoclonal IgG2 antibody produced in a mammalian cell line (Chinese hamster ovary cells) by recombinant DNA technology.
Hyperlink to the Product Information	eCTD Module 1.3.1

Indication(s) in the EEA	Current: 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: Not applicable
Dosage in the EEA	Current: **General recommendations:** Supplementation of at least 500 mg calcium and 400 IU vitamin D daily is required in all patients, unless hypercalcaemia is present. **Prevention of skeletal related events in adults with advanced malignancies involving bone** The recommended dose is 120 mg administered as a single subcutaneous injection once every 4 weeks into the thigh, abdomen or upper arm. **Giant cell tumour of bone** The recommended dose of ENWYLMA 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. Patients in the phase II study executed with the reference product Xgeva® who underwent complete resection of giant cell tumour of bone did receive an additional 6 months of treatment following the surgery as per study protocol.
	Proposed: Not applicable
Pharmaceutical form(s) and strength(s)	Current: Solution for injection. Each vial contains 120 mg of denosumab in 1.7 mL of solution (70 mg/mL).
	Proposed: Not applicable
Will the product be subject to additional monitoring in the EU?	Yes

PART II: Safety Specification

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

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

PART II: Non-clinical part of the safety specification

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

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

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

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

PART II: Module SIII - Clinical trial exposure

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

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

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

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

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

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

Demographic and Baseline Characteristics
Safety Population

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

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

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

Demographics and Baseline Characteristics – Main Treatment Period
Safety Analysis Set

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

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

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

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

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

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

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

Demographics and Baseline Characteristics – Main Treatment Period
Safety Analysis Set

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

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

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

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

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

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

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

Demographics and Baseline Characteristics – Main Treatment Period
Safety Analysis Set

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

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

Table 7. Cumulative subject exposure to MB09 from clinical trial MB09-C-01-19 by baseline height, weight and BMI - Transition period

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

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

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

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

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

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

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

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

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Hypersensitivity to the active substance or to any of the excipients	Patients who are hypersensitive to denosumab or to any of the excipients should not receive this medication.	No	It is a contraindication in the SmPC.
Unhealed lesions from dental or oral surgery	It is considered as a risk factor for the development of ONJ.	No	It is a contraindication in the SmPC.

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

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

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

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

Type of special population	Exposure
Elderly patients	Refer to PART II: Module SIII (Table 1, 2 and 3)
Pregnant or breastfeeding women	Not included in the clinical development programme
Patients with relevant comorbidities: – Patients with hepatic impairment – Patients with renal impairment	Not included in the clinical development programme
Population with relevant different ethnic origin	There is no preclinical or clinical data to date suggesting differences in the angiogenic pathway and mode of action of VEGF in patients of different ethnic origin.
Subpopulations carrying known and relevant polymorphisms	Not included in the clinical development programme

PART II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

Not applicable since this is the first Risk Management Plan.

SV.1.1 Method used to calculate exposure

Not applicable since this is the first Risk Management Plan.

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

Potential for misuse for illegal purposes

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

PART II: Module SVII - Identified and potential risks

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

ENWYLMA is a biosimilar product to the reference medicinal product Xgeva® [3]. Therefore, the safety profile of ENWYLMA is based on the general safety profile of denosumab, which resulted from the extensive experience with Xgeva® (authorised in the EU on 05 August 2011).

Overall, the development programme for ENWYLMA did not raise new safety concerns and all clinically relevant adverse effects reported in the respective clinical studies corresponded to the known safety profile of denosumab (for full information on reported adverse events within the clinical development programme for ENWYLMA, refer to eCTD Module 2.7.4 Summary of Clinical Safety). The immunogenicity of ENWYLMA was investigated as part of its clinical development programme and no differences in immunogenicity were observed compared with Xgeva®. Immunogenicity is not a safety concern of ENWYLMA, and it does not represent a newly raised safety concern for ENWYLMA.

This RMP for ENWYLMA is consequently based on the RMP for Xgeva® (version 36, 11 December 2020)

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

According to RMP for Xgeva® (version 36, 11 Decemeber 2020) no risks are considered for inclusion in this section.

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

All safety concerns in the RMP for the biosimilar product ENWYLMA are solely based on the safety concerns for Xgeva®, containing denosumab.

Important identified risks:

- Osteonecrosis of the jaw
- Atypical femoral fracture
- Hypercalcemia 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

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

Not applicable

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

SVII.3.1.1 INFORMATION ON IMPORTANT IDENTIFIED RISKS

SVII. 3.1.1.1 Osteonecrosis of the jaw

Potential mechanism(s):

Osteonecrosis of the jaw (ONJ) appears to be multifactorial and multiple hypotheses have been postulated and have included factors such as inhibition of bone remodelling, infection and inflammation, inhibition of angiogenesis, soft tissue toxicity, altered immunity and genetic predisposition. As yet, evidence supporting these hypotheses has been variable and little is understood in how these multiple pathways might interact [6;17]

Evidence source(s) and strength of evidence:

This risk was identified in randomized, controlled, phase III clinical trials. This risk was further supported by post marketing reports.

Characterisation of the risk:

Frequency

In the pooled pivotal SRE Solid Tumour studies, the subject incidence of positively adjudicated adverse events of ONJ was 1.8% in the denosumab group and 1.3% in the

zoledronic acid group; the hazard ratio was 1.38 (95% CI: 0.91, 2.11). In the SRE multiple myeloma study, the subject incidence of positively adjudicated adverse events of ONJ was 4.1% in the denosumab group and 2.8% in the zoledronic acid group; the hazard ratio was 1.47 (95% CI: 0.88, 2.48).

In clinical trials, the incidence of ONJ was higher with longer duration of exposure (Xgeva® SmPC, May 2018).

In Study 20101363, a non-interventional post marketing observational study of 2877 patients with cancer treated with Xgeva® or zoledronic acid for SRE prevention, the incidence rates (95% CI) of medically confirmed ONJ per 100 person-years were 3.0 (2.3, 3.7) in the Xgeva® inception cohort, 1.0 (0.6, 1.5) in the zoledronic acid inception cohort, and 4.3 (2.8, 6.3) in the Xgeva®-switch cohort (this cohort included patients who switched to Xgeva® after having started antiresorptive therapy with bisphosphonates for SRE prevention of no more than 2 years' net duration).

Severity

Most events leading to adjudication as ONJ were assessed as moderate to severe. Life-threatening events have been reported.

Reversibility

In general, ONJ events are clinically reversible. The majority of ONJ cases resolve with denosumab treatment interruption or discontinuation. Surgical treatment may be required; bone resection is not usually necessary.

Long-term outcomes

No data on long-term outcomes are available.

Impact on quality of life

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

Risk factors and risk groups:

Risk factors associated with ONJ include the use of antiresorptives (particularly amino bisphosphonates delivered by intravenous [IV] dosing), older age, poor dental hygiene, periodontal disease, invasive dental procedures, trauma from poorly fitting dentures, malignancy, chemotherapy (including antiangiogenesis agents such as bevacizumab), radiation to head and neck, corticosteroids, hypercoagulable state secondary to underlying malignancy, smoking and vascular insufficiency due to thrombosis [7; 16; 33; 38]

Preventability:

A dental examination with appropriate preventive dentistry is recommended prior to treatment with ENWYLMA, especially in patients with risk factors. While on treatment, patients should avoid invasive dental procedures where possible. Patients who are suspected of having or who develop ONJ while on MB09 should receive care by a dentist or an oral surgeon. In patients who develop ONJ during treatment with MB09, a temporary interruption of treatment should be considered based on individual risk/benefit assessment until the condition resolves. Good oral hygiene practices should be maintained during treatment with ENWYLMA and dental health should be monitored.

Impact on the risk-benefit balance of the product:

The risk of ONJ events has been considered in the product benefit-risk assessment. In light of the product labelling and a patient reminder card that has been proposed to minimize this risk, the overall benefit-risk balance is considered to be positive.

Public health impact:

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.

SVII. 3.1.1.2 Atypical Femoral Fracture

Potential mechanism(s):

Prolonged suppression of bone turnover may be associated with increased risk of atypical femoral fracture (AFF), but the pathogenesis remains unclear and causes of AFF are likely multifactorial. Based on nonclinical studies of bisphosphonates, 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 [27; 40]

Evidence source(s) and strength of evidence:

This risk was identified in randomized, controlled, phase III clinical trials and in open-label, phase II clinical trials. This risk was further supported by post marketing reports of Xgeva®.

Characterisation of the risk:

Frequency

In a comprehensive evaluation of denosumab 120 mg clinical trials, 15 subjects experienced 17 events meeting the American Society for Bone and Mineral Research criteria for AFF. This corresponds to 0.2% (15 of 8342) of all subjects who received at least 1 dose of denosumab (Similar results are observed when consideration is limited to studies utilizing monthly dosing throughout [0.1%, 6 subjects with AFF in 6101 subjects]). AII of these adjudicated events of AFF occurred in subjects who received denosumab 120 mg for at least 4 years corresponding to 0.7% (15 of the 2228) of subjects who were followed for 4 or more years.

In the clinical trial program, AFF has been reported uncommonly in patients treated with Xgeva® 120 mg and the risk increased with longer duration of treatment. Events have occurred during treatment and up to 9 months after treatment was discontinued.

Severity

Atypical femoral fracture is a medically important adverse event that generally requires significant medical interventions such as surgery and ongoing monitoring to mitigate risk for and severity of contralateral fractures.

Reversibility

It is unknown if the pathophysiological mechanism(s) contributing to the development of AFF are reversible after treatment is discontinued.

Long-term outcomes

No data on long-term outcomes are available.

Impact on quality of life

As with other hip 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 [11; 42]

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 [21; 34]. Atypical femoral fractures have also been reported in patients with certain comorbid conditions (e.g., vitamin D deficiency, rheumatoid arthritis [RA], hypophosphatasia) and with use of bisphosphonates, glucocorticoids, and proton pump inhibitors [40]

Preventability:

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

Impact on the risk-benefit balance of the product:

The risk of AFF events has been considered in the product benefit-risk assessment. In light of the product labelling that has been proposed to minimize this risk, the overall benefit-risk balance is considered to be positive.

Public health impact:

Based on the frequency of AFF, the size of the indicated populations, and usage patterns of denosumab in clinical practice, no significant additional public health impact is expected.

SVII. 3.1.1.3 Hypercalcemia Several Months After the Last Dose in Patients With Giant Cell Tumour of Bone and in Patients With Growing Skeletons

Potential mechanism(s):

The mechanism(s) of hypercalcemia several months after the last dose of denosumab in patients with 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 tumors and even at sites of distant metastases [10; 20; 43]. 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 such as in patients with a growing skeleton. 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 tumors themselves that have partially ossified in the cases of the adult patients with tumor recurrence via an autocrine/paracrine mechanism [13]

- 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 skeleton 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 signalling pathways (e.g., parathyroid hormone-related protein) in GCTB.

Evidence source(s) and strength of evidence:

This risk was identified in phase II clinical trials of adolescent and adult patients with GCTB, and in postmarketing reports of paediatric patients using denosumab for unauthorized indications.

Characterisation of the risk:

Frequency

Based on the 4 relevant clinical trial case reports (2 adults and 2 adolescents) identified from the completed Amgen clinical Study 20062004 of subjects with GCTB (526 subjects having received at least 1 dose of Xgeva®), the frequency of hypercalcemia in patients with GCTB following discontinuation of Xgeva® is 0.8 events per 100 subjects which corresponds to an uncommon frequency (≥ 0.1 and < 1 event per 100 subjects).

In addition, clinically significant cases of post-treatment hypercalcemia have been identified from literature case reports of denosumab use in paediatric patients for unapproved indications such as fibrous dysplasia, aneurysmal bone cysts, and juvenile Paget's disease.

Severity

In the GCTB study from Xgeva®, the events of hypercalcemia in the 4 subjects from Study 20062004 were considered grade 2, 3, or 4 in severity. All subjects had acute renal injury, and all were hospitalized. Three of 4 subjects had more than 1 event. The severity of the events in the postmarketing literature case reports appears qualitatively similar.

Reversibility

Hypercalcemia is reversible with appropriate supportive therapy.

Long-term outcomes

No data on long-term outcomes are available.

Impact on quality of life

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 MB09. In general, the most common cause of hypercalcemia in humans is hyperparathyroidism, particularly among women and individuals aged 65 years or older [35]. 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 [32; 35]

Preventability:

No preventive measures are known. Monitor patients for signs and symptoms of hypercalcemia and treat appropriately. Periodic serum calcium assessments should be given to at-risk patients as clinically indicated. The need for calcium and vitamin D supplementation should be reassessed if denosumab is discontinued.

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 labelling that has been proposed to minimize this risk, the overall benefit-risk balance is considered to be positive.

Public health impact:

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.

SVII.3.1.2 INFORMATION ON IMPORTANT POTENTIAL RISKS

SVII 3.1.2.1 Cardiovascular Events

Potential mechanism(s):

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 CV events is a regulatory concern based on the epidemiological association between OPG levels and CV disease in man. Clinical data have not substantiated a cause-and-effect between OPG and atherosclerotic processes nor between denosumab or inhibition of RANKL and undesirable CV outcomes.

Characterisation of the risk:

Frequency

In the pooled pivotal SRE Solid Tumour studies from Xgeva®, subject incidence of CV adverse events was 29.7% in both treatment groups; the hazard ratio was 0.98 (95% CI: 0.89, 1.08).

In a pivotal study with denosumab 120 mg Q4W in subjects with CRPC (Study 20050147 from Xgeva®), the subject incidence of CV adverse events was 33.1% in the denosumab group and 27.0% in the placebo group; the hazard ratio was 1.23 (95% CI: 1.02, 1.49).

In the SRE multiple myeloma study from Xgeva®, the subject incidence of adverse events of cardiac disorders was 11.6% in the denosumab group and 13.5% in the zoledronic acid group; the hazard ratio was 0.85 (95% CI: 0.65, 1.12). The subject incidence of adverse events of vascular disorder was 20.9% in the denosumab group and 19.8% in the zoledronic acid group; the hazard ratio was 1.07 (95% CI: 0.86, 1.31).

Severity

The majority of CV events were mild to moderate. Life-threatening and fatal events have been reported.

Reversibility

No data on reversibility are available.

Long-term outcomes

No data on long-term outcomes are available.

Impact on quality of life

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

Risk factors and risk groups:

The denosumab development program comprises studies of older subject populations (e.g., osteoporosis, cancer) that are likely to have a higher incidence of pre-existing CV conditions and, thus, a higher incidence of CV toxicities than that of the general population [23; 39]

Risk factors for atherosclerosis include age, gender, ethnicity, family history, elevated lipid levels, cigarette smoking, hypertension, diabetes, and concomitant medications, including antipsychotic agents and cyclooxygenase-2 (COX-2) inhibitors [37; 41]

Preventability:

Based on clinical data to date, denosumab has not been associated with an increased incidence or severity of CV adverse effects; therefore, no preventive measures are defined.

Patients with potential CV events should be managed according to usual standards of care.

Impact on the risk-benefit balance of the product:

The risk of CV events has been considered in the product benefit-risk assessment, and the overall benefit-risk balance is considered to be positive.

Public health impact:

Significant public health impact on CV disease severity or incidence is not expected based on the information from denosumab clinical studies in the advanced cancer and postmenopausal osteoporosis (PMO)/hormone ablation therapy (HALT) settings.

SVII.3.1.2.2 Malignancy

Potential mechanism(s):

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. The results of Study 20170728, a post marketing 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 Xgeva®.

Characterisation of the risk:

Frequency

In the primary, double-blind treatment phases of IV phase III active-controlled clinical trials in patients with advanced malignancies involving bone, NPM was reported in 54/3691 (1.5%) of patients treated with Xgeva® (median exposure of 13.8 months; range: 1.0 to 51.7) and 33/3688 (0.9%) of patients treated with zoledronic acid (median exposure of 12.9 months; range: 1.0 to 50.8). The cumulative incidence at 1 year was 1.1% for denosumab and 0.6% for zoledronic acid, respectively.

In the SRE multiple myeloma study from Xgeva®, the subject incidence of adverse events of NPM was 2.6% in the denosumab group and 1.4% in the zoledronic acid group; the hazard ratio was 1.81 (95% CI: 0.90, 3.66). Subjects who had new malignancies in this study

generally had underlying risk factors for malignancy and no pattern was apparent in the types of new primary malignancies.

In clinical Study 20062004 in GCTB from Xgeva®, based on medical review and a data cut-off date of the final analysis of 15 August 2018, a total of 20 subjects (3.8%; N = 526) developed new malignancy in GCTB. Of these 20 subjects, 9 subjects developed new malignancies that were unrelated to GCTB: 2 events (0.4%) of ductal breast carcinoma and single events of each, adenocarcinoma of colon, breast cancer stage 1, neoplasm, oesophageal adenocarcinoma, osteosarcoma, papillary thyroid cancer, renal cancer, rhabdomyosarcoma, and thyroid cancer. A total of 11 subjects (2.1%) developed new malignancy in GCTB: 5 subjects were deemed to have had primary malignant GCTB, 5 subjects were assessed to have had sarcomatous transformation, and 1 subject had secondary malignant GCTB (post-radiation).

In Study 20170728, a retrospective observational cohort study of 9710 patients with bone metastases from breast, prostate, or lung cancer treated with Xgeva® or IV zoledronic acid, the overall rate of NPM for the breast cancer cohort was 11.5 per 1000 person-years of follow-up (PY) in the Xgeva® group and 16.2 per 1000 PY in the zoledronic acid group; for the prostate cancer cohort was 19.6 per 1000 PY in the Xgeva® group and 20.1 per 1000 PY in the zoledronic acid group; and for the lung cancer cohort was 9.5 per 1000 PY in the Xgeva® group and 11.5 per 1000 PY in the zoledronic acid group.

The 3-year cumulative incidence of NPM for the breast cancer cohort was 0.022 (95% CI: 0.014, 0.035) in the Xgeva® group and 0.032 (95% CI: 0.023, 0.045) in the zoledronic acid group; for the prostate cancer cohort was 0.034 (95% CI: 0.026, 0.044) in the Xgeva® group and 0.036 (95% CI: 0.026, 0.049) in the zoledronic acid group; and for the lung cancer cohort was 0.007 (95% CI: 0.004, 0.012) in the Xgeva® group and 0.008 (95% CI: 0.005, 0.014) in the zoledronic acid group.

Severity

Not applicable.

Reversibility

No data on reversibility are available.

Long-term outcomes

No data on long-term outcomes are available.

Impact on quality of life

Malignancy is typically disabling and may require surgery, chemotherapy, and/or radiotherapy.

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.

Preventability:

Second malignant neoplasms have become increasingly recognized and current recommendations include vigilance for these cancers in adult cancer survivors.

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 labelling that has been proposed to minimize this risk, the overall benefit-risk balance is considered to be positive.

Public health impact:

Significant public health impact is not expected based on the information from studies in the PMO/HALT and advanced cancer settings.

SVII 3.1.2.3 Delay in Diagnosis of Primary Malignancy in Giant Cell Tumour of Bone

Potential mechanism(s):

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 regulatory concern based on the difficulties in diagnosing PMGCTB in Study 20062004 from Xgeva® studies.

Characterisation of the risk:

Frequency

In clinical studies in GCTB from Xgeva®, based on medical review, 11 subjects (2.1%; N=523) had GCTB bone malignancies. Of these, 5 subjects (1.0%) had PMGCTB.

	Time to PMGCTB
Number of cases	5
Mean time (Q1, Q3) to malignancy (months)[a]	19.12 (11.99,24.18)
Median (min, max) denosumab exposure (months)	8.44 (2.8,14.8)

[a] Time from diagnosis of GCTB to diagnosis of malignancy of GCTB

Source: Table GCTB table 200-6.21.06

Severity

Not applicable.

Reversibility

Not applicable.

Long-term outcomes

No data on long-term outcomes are available.

Impact on quality of life

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.

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 labelling that has been proposed to minimize this risk, the overall benefit-risk balance is considered to be positive.

Public health impact:

Given that GCTB is very rare condition, no impact on public health is expected.

SVII 3.1.2.4 Hypercalcemia Several Months After the Last Dose in Patients Other Than Those with Giant Cell Tumour of Bone or Growing Skeletons

Potential mechanism(s):

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 RANKL allows for terminal differentiation and activation of osteoclasts, which were suppressed during treatment. In patients with underlying causes for calcium dyscrasias (i.e., subclinical hyperparathyroidism), denosumab discontinuation, with its transient increase in bone remodelling 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

Cases of hypercalcemia in the off-treatment period have been reported in clinical studies, but given the disease state of the subjects, as well as other confounding factors, the occurrence of hypercalcemia in patients other than those with GCTB or with growing skeletons cannot be attributed to discontinuation of Xgeva® based on available information. As the mechanism for the identified risk in the susceptible populations is not well understood, a theoretical risk remains in other patient groups.

Severity

Not applicable.

Reversibility

No data on reversibility are available.

Long-term outcomes

No data on long-term outcomes are available.

Impact on quality of life

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 Xgeva®.

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.

Public health impact:

No significant public health impact is expected as the potential events remain infrequent despite extensive market exposure.

SVII.3.2 Presentation of the Missing Information

SVII. 3.2.1 Patients with Prior intravenous Bisphosphonate Treatment

Evidence source

The incidence of ONJ in patients with prior IV bisphosphonate use was similar to that of patients who only received Xgeva® in the completed Study 20101363. No notable association was evident between ONJ and prior use of bisphosphonates.

Population in need of further characterization

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.

SVII.3.2.2 Safety with Long-term Treatment and With Long-term Follow-up After Treatment in Adults and Skeletally Mature Adolescents With GCTB

Evidence source

The overall safety profile of Xgeva® in the completed Study 20062004 was similar to the safety profile of Xgeva® observed in the treatment of subjects with advanced cancer and bone metastases.

Population in need of further characterization

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.

SVII. 3.2.3 Off-label Use in Patients with GCTB That is Resectable Where Resection is Unlikely to Result in Severe Morbidity

Evidence source

No formal studies have been completed to determine Xgeva's® effect on off-label use in patients with GCTB that is resectable where resection is unlikely to result in severe morbidity.

Population in need of further characterization

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 safety concerns

Table 7. Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Osteonecrosis of the jaw • Atypical femoral fracture • Hypercalcemia several months after the last dose in patients with giant cell tumor of bone and in patients with growing skeletons
Important potential risks	• Cardiovascular events • Malignancy • Delay in diagnosis of primary malignancy in giant cell tumor of bone • Hypercalcemia several months after the last dose in patients other than those with giant cell tumor 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 tumor of bone • Off-label use in patients with giant cell tumor 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 reaction reporting and signal detection are presented in Table 8.

Table 8. Specific Adverse Reaction Follow-up Questionnaires

Follow-up Questionnaire (Annex 4. Specific Adverse Drug Reaction Follow-up Forms)	Safety Concern(s)	Purpose
Potential Osteonecrosis Of the Jaw	Osteonecrosis of the Jaw	To monitor the reporting rate and nature of ONJ in patients treated with denosumab in the postmarketing environment.
Potential atypical fracture	Atypical femoral fracture	To monitor the reporting rate and nature of AFF in patients treated with denosumab in the postmarketing environment.

III.2 Additional pharmacovigilance activities

The pharmacovigilance plan does not include any additional pharmacovigilance activities.

III.3 Summary table of additional pharmacovigilance activities

Not applicable.

PART IV: Plans for post-authorisation efficacy studies

Not applicable

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

Risk minimisation plan

V.1 Routine risk minimisation measures

Table 9. Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Important Identified Risks	
Osteonecrosis of the jaw	Routine risk communication: • SmPC Section 4.3 • SmPC Section 4.4 • SmPC Section 4.8 • SmPC Section 5.1 • PIL Section 2 • PIL Section 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendations for oral examination, maintenance of good oral hygiene during treatment, management of patients with unavoidable invasive dental procedure, and temporary interruption of treatment if ONJ occurs are included in Section 4.4 of SmPC. Other risk minimization measures beyond the PI: • Legal status: ENWYLMA is a medicinal product subject to restricted medical prescription.
Atypical femoral fracture	Routine risk communication: • SmPC Section 4.4 • SmPC Section 4.8 • PIL Section 2 • PIL Section 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendation for reporting new or unusual thigh, hip, or groin pain is included Section 4.4 of SmPC. Other risk minimization measures beyond the PI:

Safety concern	Routine risk minimisation activities
Important Identified Risks	
	• Legal status: ENWYLMA is a medicinal product subject to restricted medical prescription.
Hypercalcemia several months after the last dose in patients with giant cell tumor of bone and in patients with growing skeletons	Routine risk communication: • SmPC Section 4.4 • SmPC Section 4.8 • PIL Section 2 • PIL Section 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendations for monitoring the patients for signs and symptoms of hypercalcaemia after discontinuation of ENWYLMA treatment are included in Section 4.4 of SmPC and Section 4 of the PIL Other risk minimization measures beyond the PI: • Legal status: ENWYLMA is a medicinal product subject to restricted medical prescription.

Important Potential Risks	
Cardiovascular events	Routine risk communication: • Not applicable Other risk minimization measures beyond the PI: • Legal status: ENWYLMA is a medicinal product subject to restricted medical prescription.
Malignancy	Routine risk communication: • SmPC Section 4.4 • SmPC Section 4.8 • SmPC Section 5.1 • PIL Section 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendations for monitoring the patients for radiological signs of malignancy, new malignancy, or osteolysis are included in Section 4.4 of SmPC. Other risk minimization measures beyond the PI:

	• Legal status: ENWYLMA is a medicinal product subject to restricted medical prescription.
Delay in diagnosis of primary malignancy in giant cell tumor of bone	Routine risk communication: • Not applicable Other risk minimization measures beyond the PI: • Legal status: ENWYLMA is a medicinal product subject to restricted medical prescription
Hypercalcemia several months after the last dose in patients other than those with GCTB or growing skeletons	Routine risk communication: • Not applicable Other risk minimization measures beyond the PI: • Legal status: ENWYLMA is a medicinal product subject to restricted medical prescription.

Missing Information	
Patients with previous intravenous treatment with bisphosphonate treatment	Routine risk communication: • SmPC Section 4.5 • SmPC Section 5.1 • PIL Section 2 Other risk minimization measures beyond the PI: • Legal status: ENWYLMA is a medicinal product subject to restricted medical prescription.
Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with GCTB	Routine risk communication: • Not applicable Other risk minimization measures beyond the PI: • Legal status: ENWYLMA is a medicinal product subject to restricted medical prescription.
Off-label use in patients with GCTB that is resectable where resection is unlikely to result in severe morbidity	Routine risk communication: • Not applicable Other risk minimization measures beyond the PI: • Legal status: ENWYLMA is a medicinal product subject to restricted medical prescription.

V.2 Additional risk minimisation measures

Patient Reminder Card

Objectives	Patient reminder cards will be provided to address the following risk: • Osteonecrosis of the jaw
Rationale for the additional risk minimization activity	The purpose of the patient reminder card is to remind patients about important safety information that they need to be aware of before and during treatment with denosumab (ENWYLMA) injections for cancer-related conditions, including: • the risk of osteonecrosis of the jaw during treatment with ENWYLMA; • the need to highlight any problems with their mouth or teeth to their doctors/nurses before starting treatment; • the need to ensure good oral hygiene and receive routine dental check-ups during treatment; • the need to inform their dentist of treatment with ENWYLMA and to contact their doctor or dentist immediately if problems with the mouth or teeth occur during treatment.
Target audience and planned distribution path	Target audience will be the patients. The patient reminder card is distributed to prescribers with instruction to provide it to patients. The patient reminder card is distributed by mail and prescribers are provided with contact details to request additional copies of the card. Some national plans include making the patient reminder card available on a website.
Plans to evaluate the effectiveness of the interventions and criteria for success	Monitor and evaluate post marketing and clinical study safety data and report in periodic safety updated reports (PSURs). The distribution of the patient reminder card will be tracked to ensure that it is distributed in accordance with the plan agreed with national agencies. Additional requests for patient reminder cards and web downloads will also be recorded as an indicator of ongoing use of the patient reminder card. The effectiveness of risk minimization of ONJ in the EU will be monitored through postmarketing reporting rates of ONJ before and after introduction of the patient reminder card compared to the rest of the world. In addition, the focused questionnaire for postmarketing reports of ONJ presented in Annex 4. Specific Adverse Drug Reaction Follow-up Forms will

	be revised to permit inclusion of data on whether the patient affected by ONJ had previously received a patient reminder card or not.
Evaluation of the effectiveness of the risk minimization activities	No change in risk-benefit profile
Removal of additional risk minimization activities	Not applicable

V.3 Summary of risk minimisation measures

Table 10. 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 Section 4.3 • SmPC Section 4.4, where recommendations for oral examination, maintenance of good oral hygiene, management of patients with unavoidable invasive dental procedure, and temporary interruption are discussed. • SmPC Section 4.8 • SmPC Section 5.1 • PIL Section 2, where recommendations for oral examination, maintenance of good oral hygiene, management of patients with unavoidable invasive dental procedure, and sign of ONJ are discussed. • PIL Section 4, where symptoms of ONJ is discussed. Additional risk minimization measures • Patient reminder cards	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Denosumab core questionnaire - Osteonecrosis of the Jaw • Potential events of ONJ, reported in ongoing clinical trials, are adjudicated by a panel of external medical experts. • Potential events of ONJ reported in the post marketing setting are medically reviewed internally to determine if the ONJ events meet the AAOMS ONJ case definition. Additional pharmacovigilance activities: • None
Atypical femoral fracture	Routine risk minimisation measures: • SmPC Section 4.4, where recommendations for reporting new or unusual thigh, hip, or groin pain is discussed. • SmPC Section 4.8 • PIL Section 2, where recommendations for reporting	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Denosumab core questionnaire – Post marketing reports of potential atypical fracture. • Potential cases of AFF from clinical trial setting are

	new or unusual pain in your thigh, hip, or groin is discussed. • PIL Section 4, where signs of thigh bone fracture are discussed. Additional risk minimization measures • None	adjudicated by an independent committee that is blinded to treatment. • Potential cases of AFF from post marketing setting are medically reviewed internally based on diagnosis of the radiographic findings and without requiring the radiographs to be sent to Amgen. 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 4.4 where recommendations for monitoring the patients for signs and symptoms of hypercalcaemia after discontinuation of ENWYLMA is discussed. • SmPC Section 4.8 • PIL Section 2, where recommendations for monitoring the patients for signs and symptoms of hypercalcemia after discontinuation of ENWYLMA treatment is discussed. • PIL Section 4 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Important Potential Risks		

Cardiovascular events	No risk minimization measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Malignancy	Routine risk minimisation measures: • SmPC Section 4.4, where recommendations for monitoring the patients for radiological signs of malignancy, new malignancy, or osteolysis is discussed. • SmPC Section 4.8 • SmPC Section 5.1 • PIL Section 4 Additional risk minimization measures • None	Routine pharmacovigilance beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities • None
Delay in diagnosis of primary malignancy in giant cell tumour of bone	No risk minimization measures	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 GCTB or growing skeletons	No risk minimization measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities • None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Missing Information		
Patients with prior intravenous bisphosphonate treatment	Routine risk minimisation measures: • SmPC Section 4.5 • SmPC Section 5.1 • PIL Section 2 Additional risk minimization 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	No risk minimization measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities • None
Off-label use in patients with GCTB that is resectable where resection is unlikely to result in severe morbidity	No risk minimization measures	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 ENWYLMA (denosumab)

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

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

This summary of the RMP for ENWYLMA 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 ENWYLMA RMP.

I. The medicine and what it is used for

ENWYLMA 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 and 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 as the active substance and it is given by subcutaneous injection.

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

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

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

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

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;

- The authorized pack size -the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the public (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

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

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

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

II.A List of important risks and missing information

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

Summary of safety concerns	
Important identified risks	• Osteonecrosis of the jaw • Atypical femoral fracture • Hypercalcemia several months after the last dose in patients with giant cell tumor of bone and in patients with growing skeletons
Important potential risks	• Cardiovascular events • Malignancy • Delay in diagnosis of primary malignancy in giant cell tumor of bone

	• Hypercalcemia several months after the last dose in patients other than those with giant cell tumor 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 tumor of bone • Off-label use in patients with giant cell tumor of bone that is resectable where resection is unlikely to result in severe morbidity.

II.B Summary of important risks

Important Identified risk 1: Osteonecrosis of the Jaw	
Evidence for linking the risk to the medicine	This risk was identified in randomized, controlled, phase III clinical trials. This risk was further supported by postmarketing reports.
Risk factors and risk groups	Risk factors associated with osteonecrosis of the jaw (ONJ) include the use of antiresorptives (particularly aminobisphosphonates delivered by intravenous [IV] dosing), older age, poor dental hygiene, periodontal disease, invasive dental procedures, trauma from poorly fitting dentures, malignancy, chemotherapy (including antiangiogenesis agents such as bevacizumab), radiation to head and neck, corticosteroids, hypercoagulable state secondary to underlying malignancy, smoking and vascular insufficiency due to thrombosis [7 ; 16; 33; 38]
Risk minimisation measures	Routine risk minimization measures: • SmPC Section 4.3, 4.4, 4.8 and 5.1 • Patient information Leaflet (PIL) Section 2 and 4 Additional risk minimization measures: • Patient reminder card
Additional pharmacovigilance activities:	None.

Important Identified risk 2: Atypical Femoral Fracture	
Evidence for linking the risk to the medicine	This risk was identified in randomized, controlled, phase III clinical trials and in open-label, phase II clinical trials. This risk was further supported by postmarketing reports.
Risk factors and risk groups	Long-term antiresorptive treatment has been associated with atypical femoral fracture (AFF). Corticosteroids have also been reported in the literature to potentially be associated with AFF [21; 34]. Atypical femoral fractures have also been reported in patients with certain comorbid conditions (e.g., vitamin D deficiency, rheumatoid arthritis [RA], hypophosphatasia) and with use of bisphosphonates, glucocorticoids, and proton pump inhibitors [40]
Risk minimisation measures	Routine risk minimization measures: • SmPC Section 4.4, and 4.8 • PL Section 2 and 4 Additional risk minimization measures: • None
Additional pharmacovigilance activities:	None.

Important Identified risk 3: Hypercalcemia Several Months After the Last Dose in Patients with Giant Cell Tumor of Bone and in Patients with Growing Skeletons	
Evidence for linking the risk to the medicine	This risk was identified in phase II clinical trials of adolescent and adult patients with giant cell tumour of bone (GCTB), 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 Xgeva®. In general, the most common cause of hypercalcemia in humans is hyperparathyroidism, particularly among women and individuals aged 65 years or older [35]. 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 [32; 35]
Risk minimisation measures	Routine risk minimization measures: • SmPC Section 4.4 and 4.8 • PIL Section 2 and 4 Additional risk minimization measures: • None
Additional pharmacovigilance activities	None.

Important Potential risk 1: Cardiovascular Events	
Evidence for linking the risk to the medicine	The risk of cardiovascular events is a regulatory concern based on the epidemiological association between osteoprotegerin (OPG) levels and cardiovascular disease in man. Clinical data have not substantiated a cause-and-effect between OPG and atherosclerotic processes nor between denosumab or inhibition of receptor activator of nuclear factor kappa B-ligand (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 [23; 41] Risk factors for atherosclerosis include age, gender, ethnicity, family history, elevated lipid levels, cigarette smoking, hypertension, diabetes, and concomitant medications, including antipsychotic agents and cyclooxygenase-2 (COX-2) inhibitors [37; 41].
Risk minimisation measures	Routine risk minimization measures: • None Additional risk minimization measures:

	• None
Additional pharmacovigilance activities	None.

Important Potential risk 2: Malignancy	
Evidence for linking the risk to the medicine	Imbalance is observed in the new primary malignancy (NPM) events between the zoledronic acid and Xgeva® treatment groups in the pivotal clinical studies. The results of Study 20170728, a 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 Xgeva®.
Risk factors and risk groups	General factors for increasing risk of new primary malignancy 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.
Risk minimisation measures	Routine risk minimization measures: • SmPC Section 4.4, 4.8 and 5.1 • PL Section 4 Additional risk minimization measures: • None
Additional pharmacovigilance activities:	None.

Important potential risk 3: Delay in Diagnosis of Primary Malignancy in Giant Cell Tumour of Bone	
Evidence for linking the risk to the medicine	The risk of delay in diagnosis of primary malignancy in giant cell tumour of bone is a regulatory concern based on difficulties in diagnosing primary malignancy in giant cell tumour of bone (PMGCTB).

	This safety concern was identified in the clinical trial setting.
Risk factors and risk groups	Patients with GCTB are known to be at risk for PMGCTB.
Risk minimisation measures	Routine risk minimization measures: • None Additional risk minimization measures: • None
Additional pharmacovigilance activities:	None.

Important potential risk 4: 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 minimization measures: • None Additional risk minimization measures: • None
Additional pharmacovigilance activities	None.

Missing information: Patients with Previous Intravenous Treatment with Bisphosphonate Treatment	
Risk minimisation measures	Routine risk minimization measures: • SmPC Section 4.5 and 5.1 • PIL Section 2 Additional risk minimization measures: • None

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

Missing information: Off label use in patients with giant cell tumour of bone that is resectable where resection is unlikely to result in severe morbidity	
Risk minimisation measures	Routine risk minimization measures: • None Additional risk minimization 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 ENWYLMA.

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

There are no studies required for ENWYLMA.

[redacted]

Annex 4 - Specific adverse drug reaction follow-up forms

DENOSUMAB Core Questionnaire Osteonecrosis of the Jaw

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

Patient Identifier

Patient Initials

Date of Event Onset

Date of This Report

Gender: ☐Male ☐Female Weight:_____lb _____Kg

Event Reported Term

Age at time of event:_____

Study No.

☐Clinical Trial
☐Post-Marketing

Safety Database No.

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

Denosumab Indication

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

Denosumab Dose

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

Denosumab Exposure

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

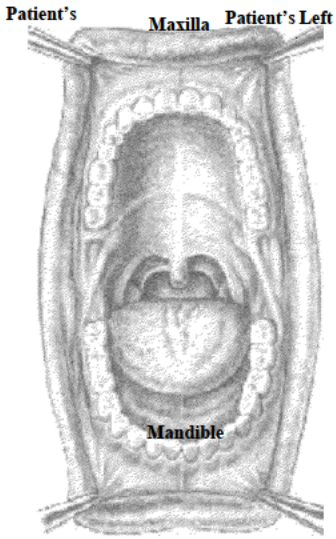
EVIDENCE OF EXPOSED BONE (Please indicate dates as DD/MM/YYYY)

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

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

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

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



Oral Findings

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

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

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

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

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

REPORTER

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

Signature

_____

Title

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

Patient Identifier	Patient Initials	Safety Database No.

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

Dental / oral surgery / stomatology consultations ☐ No ☐ Yes ☐ Unknown If yes, please give date examination _____
Please provide any consult reports, radiographs, pictures if available _____

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

Antibiotics ☐ No ☐ Yes ☐ Unknown If yes, agent(s)/route/dose _____ Start date _____ Stop date _____
Please describe outcomes of treatment _____
Oral rinses ☐ No ☐ Yes ☐ Unknown If yes, agent(s)/dose _____
Please describe outcomes of treatment _____
Oral surgery ☐ No ☐ Yes ☐ Unknown If yes, type of surgery _____
Start date _____ Stop date _____
Please describe outcomes of treatment _____
Hospitalizations ☐ No ☐ Yes ☐ Unknown If yes, reason for hospitalization _____
Hospitalization begin date _____ Hospitalization end date _____
Please describe outcomes of treatment _____

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

History of poor oral hygiene ☐ No ☐ Yes ☐ Unknown _____
Dental extraction recently ☐ No ☐ Yes ☐ Unknown If yes, Date of procedure _____
Dental surgery recently ☐ No ☐ Yes ☐ Unknown If yes, Date of procedure _____
Periodontal disease including gingival bleeding, calculus, etc. ☐ No ☐ Yes ☐ Unknown Start date _____ Stop date _____
Draining fistula in affected area ☐ No ☐ Yes ☐ Unknown Start date _____ Stop date _____
Dental abscess in affected area ☐ No ☐ Yes ☐ Unknown Start date _____ Stop date _____
Osteomyelitis in affected area ☐ No ☐ Yes ☐ Unknown Start date _____ Stop date _____
Root-canal treatment near affected area ☐ No ☐ Yes ☐ Unknown If yes, date of treatment _____
Dental treatment, surgery or tooth extraction to the involved area within the last 4-6 months PRIOR to the onset of the oral lesion
☐ No ☐ Yes ☐ Unknown
History of dentures / dental appliance / implant ☐ No ☐ Yes ☐ Unknown If yes, please specify ☐ Upper ☐ Lower
Area of lesion at or near a contact point ☐ No ☐ Yes ☐ Unknown

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

PO bisphosphonate ☐ No ☐ Yes ☐ Unknown If yes, agent(s)/dose _____
Start date _____ Stop date _____
IV bisphosphonate ☐ No ☐ Yes ☐ Unknown If yes, agent(s)/dose _____
Start date _____ Stop date _____
Glucocorticoid use within the past 12 months ☐ No ☐ Yes ☐ Unknown If yes, agent(s)/dose _____
Start date _____ Stop date _____
Immunosuppressant use within the past 12 months ☐ No ☐ Yes ☐ Unknown If yes, agent(s)/dose _____
Start date _____ Stop date _____
Chemotherapy within the past 12 months ☐ No ☐ Yes ☐ Unknown If yes, agent(s)/dose _____
Start date _____ Stop date _____
Anti-angiogenic agents (e.g. bevacizumab) within the past 12 months ☐ No ☐ Yes ☐ Unknown If yes, agent(s)/dose _____
Start date _____ Stop date _____

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

Current smoker ☐ No ☐ Yes ☐ Unknown
If yes, estimated number of pack-years _____
If past smoker, stop date _____
Alcohol consumption ☐ No ☐ Yes ☐ Unknown
If yes, estimated of drinks per week _____
Diabetes ☐ No ☐ Yes ☐ Unknown If yes, ☐ Type I ☐ Type II

E-mail Address:

REPORTER

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

Signature

Title

Date

DENOSUMAB Core Questionnaire POSTMARKETING REPORTS OF POTENTIAL ATYPICAL FRACTURE (low energy, subtrochanteric/femoral shaft fractures)

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

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

Gender: ☐ Male ☐ Female Weight:_____lb _____Kg

Age at the time of event: _____

Event

Study Number (If applicable).

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

Denosumab indication:

☐ Postmenopausal osteoporosis

☐ Bone loss from hormone ablation therapy
Please specify diagnosis_____
_____

☐ Advanced cancer with bone metastasis
Please specify cancer_____

☐ Other (please specify) _____
_____

☐ Don't know_____

Denosumab Dose:

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

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

Denosumab Exposure:

Denosumab first administered (date)_____

Last denosumab dose before event (date)_____

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

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

DIAGNOSIS (Check all that apply)

Location of fracture:
☐ Femur neck
☐ Femur distal
☐ Femur midshaft
☐ Femur intertrochanter
☐ Femur subtrochanter
☐ Other location (specified)_____

Diagnostic imaging used to confirm fracture
☐ X-ray ☐ CT scan ☐ MRI
Date of imaging at time of femur fracture (DD/MM/YYY): _____

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

Was this a pathological fracture associated with bone tumor or miscellaneous bone diseases (e.g. Paget's disease, fibrous dysplasia)
☐ Yes ☐ No ☐ Unknown

Type of fracture:
☐ Transverse
☐ Oblique
☐ Spiral
☐ Not reported

Fracture radiology report includes:

Simple transverse or oblique (30°) fracture with beaking of the cortex:
☐ Yes ☐ No ☐ Not reported

Diffuse cortical thickening of the proximal femoral shaft:
☐ Yes ☐ No ☐ Not reported

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

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

Early symptom of pain over fracture site
☐ Pain at the site at rest
☐ Pain at the site with weight bearing
☐ None

Fracture healed (union) within 6 months ☐ Yes ☐ No ☐ Unknown
If yes:
☐ Date of fracture union (DD/MM/YYY)_____
☐Patient able to walk without assistance ☐ Yes ☐ No ☐ Unknown
☐ Fracture union confirmed through imagine ☐ Yes ☐ No ☐ Unknown
If yes, check all diagnostic imaging that applies: ☐ X-ray ☐ CT scan ☐ MRI

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

Patient Identifier	Patient Initials	Date of this report

TREATMENT (Please provide dates and indicate attachments if available)

Methods to reduce and set fracture:

☐ Non-surgical reduction_____ ☐ Revision surgery (2nd surgery_____

☐ Casting_____ ☐ Other_____

☐ Surgery_____ _____ ☐ Unknown_____

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

General

☐ History or current corticosteroid use

☐ Affected hip with prior surgical pinning

☐ Affected hip with prior hip replacement

Cancer:
Evidence of any metastases ☐ Yes ☐ No ☐ Unknown
If yes, did metastasis involve bone? ☐ Yes ☐ No ☐ Unknown
Metastasis in femur where fracture occurred? ☐ Yes ☐ No ☐ Unknown

Prior osteoporosis therapy:

☐ Estrogen

☐ Selective estrogen receptor modulator (SERM)

☐ Bisphosphonate (please indicate)
☐ Intravenous ☐ Oral
If yes, how long has therapy been received? (months, years)

☐ Parathyroid hormone

Past medical and surgical history

_____

_____

_____

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

_____

_____

_____

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

_____

_____

_____

REPORTER

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

Signature_____

Title_____ **Date**_____

Office Fax:

Annex 6 - Details of proposed additional risk minimisation measures

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

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

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

Patient reminder card:

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

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

The patient reminder card will remind patient about important safety information that the need to be aware of before and during treatment with denosumab (ENWYLMA) injections for cancer-related conditions, including:

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

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

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