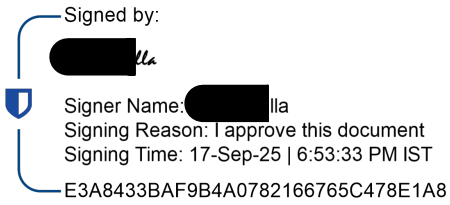
EU Risk Management Plan for Xbonzy 120 mg solution for injection (Denosumab)

RMP version to be assessed as part of this application:

RMP Version number:	0.4
Data lock point for this RMP:	17 September 2025
Date of final sign off:	17 September 2025
Rationale for submitting an updated RMP:	Invented name updated
Summary of significant changes in this RMP:	Following changes made: Invented name in the European Economic Area (EEA) updated - Xbonzy 120 mg solution for injection
Other RMP versions under evaluation:	Not applicable
Details of the currently approved RMP:	Not applicable
QPPV name:	[redacted]

QPPV signature:



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Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) **(INN or common name)**	Denosumab
Pharmacotherapeutic group(s) (ATC Code)	Pharmacotherapeutic group: Drugs for treatment of bone diseases – other drugs affecting bone structure and mineralisation. ATC code: M05BX04
Marketing Authorisation Holder	Reddy Holding GmbH
Medicinal products to which this RMP refers	01
Invented name(s) in the European Economic Area (EEA)	Proposed: • Xbonzy 120 mg solution for injection (Hereafter referred to as “Denosumab”)
Marketing authorisation procedure	Centralised (EMEA/H/C/006722/0000)
Brief description of the product	Chemical class Human immunoglobulin G2 (IgG) monoclonal antibody
	Summary of mode of action Denosumab is a IgG2 that targets and binds with high affinity and specificity to receptor activator of nuclear factor kappa-B ligand (RANKL), preventing the RANKL/receptor activator of nuclear factor kappa-B 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	Please refer to Module 1.3.1 of this Dossier

Indication(s) in the EEA	Current: Prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with advanced malignancies involving bone. Treatment of adults and skeletally mature adolescents with giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity.
	Proposed (if applicable): Not applicable.
Dosage in the EEA	Current: <u>Prevention of skeletal related events in adults with advanced malignancies involving bone</u> The recommended dose is 120 mg administered as a single subcutaneous injection once every 4 weeks into the thigh, abdomen or upper arm. <u>Giant cell tumour of bone</u> The recommended dose is 120 mg administered as a single subcutaneous injection once every 4 weeks into the thigh, abdomen or upper arm with additional 120 mg doses on days 8 and 15 of treatment of the first month of therapy.
	Proposed (if applicable): Not applicable.
Pharmaceutical form(s) and strengths	Current: Solution for injection (injection). Each vial contains 120 mg of denosumab in 1.7 mL of solution (70 mg/mL). <u>Method of administration</u> Subcutaneous injection.
	Proposed (if applicable):
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

This Module is not required for a biosimilar in accordance with Good Pharmacovigilance Practices (GVP) Module V–Risk Management Systems Table V.5., Summary of minimum RMP requirements for initial marketing authorisation applications.

Part II: Module SII - Non-clinical part of the safety specification

Denosumab has been developed as a proposed biosimilar to US-licensed Xgeva® and to EU-approved Xgeva® (the originator).

Physicochemical and functional pharmacological data generally indicated biosimilarity among multiple batches of Denosumab and the originator product, Xgeva®.

Key Safety Findings From Nonclinical Studies and Relevance to Human Usage (Xgeva **®)**

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Reproductive toxicity	Originator denosumab had no effect on female fertility or male reproductive organs in monkeys at exposures that were 9.5- to 16-fold higher, respectively, than the human exposure at 120 mg SC administered once Q4W. In a study of cynomolgus monkeys dosed with Originator denosumab during the period equivalent to the first trimester at area above the curve (MC) exposures up to 10-fold higher than the human dose (120 mg Q4W), there was no evidence of maternal or foetal harm. In this study, foetal lymph nodes were not examined. In another study of cynomolgus monkeys dosed with Originator denosumab throughout pregnancy at MC exposures 12-fold higher than the human dose (120 mg every 4-weeks), there were increased stillbirths and postnatal mortality; abnormal bone growth resulting in reduced bone strength, reduced haematopoiesis, and tooth malalignment; absence of peripheral lymph nodes; and decreased neonatal growth. There	Originator denosumab is not recommended for use in pregnant women. Women should be advised not to become pregnant during and for at least 5 months after treatment with Originator denosumab. It is not known if Originator denosumab is excreted in human milk. Because Originator denosumab has the potential to cause adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug. Use in pregnant and lactating women is not considered a safety concern in this RMP.

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
	was no evidence of maternal harm prior to labour; adverse maternal effects occurred infrequently during labour. Maternal mammary gland development was normal.	
Developmental toxicity	Originator denosumab has been shown to be a potent inhibitor of bone resorption by inhibition of RANKL. Adolescent primates dosed with Originator denosumab at 2.8 and 15 times (10 and 50 mg/kg dose) the clinical exposure based on MC had abnormal growth plates. In neonatal cynomolgus monkeys exposed in utero to Originator denosumab at 50 mg/kg, there was increased postnatal mortality; abnormal bone growth resulting in reduced bone strength, reduced haematopoiesis, and tooth malalignment; absence of peripheral lymph nodes; and decreased neonatal growth. Following a recovery period from birth out to 6 months of age, the effects on bone largely returned to normal; there were no adverse effects on tooth eruption; and minimal to moderate mineralisation in multiple tissues was seen in one recovery animal. In neonatal rats, inhibition of RANKL (target of Originator denosumab therapy) was associated with inhibition of bone growth, altered growth plates, and inhibited tooth eruption, and these changes were partially reversible upon cessation of RANKL inhibition.	The safety and efficacy of Originator denosumab have not been established in paediatric patients other than skeletally mature paediatric patients with GCTB. Treatment with Originator denosumab may impair bone growth in children with open growth plates and may inhibit eruption of dentition. Innovator Originator denosumab is not recommended for use in pregnant women. Women should be advised not to become pregnant during and for at least 5 months after treatment with Innovator denosumab

No studies to evaluate safety pharmacology and toxicity of Denosumab have been conducted in accordance with the European Economic Area (EMA) and Food and Drug Administration (FDA) guidance for development of biosimilar.

Part II: Module SIII - Clinical trial exposure

Two (2) company-sponsored (Alvotech-partner) clinical trials have been conducted with denosumab since the Development International Birth Date (DIBD).

Completed studies:

AVT03-GL-P01

A randomised, double-blind, single-dose, parallel-group design, 2-arm study comparing the pharmacokinetic, pharmacodynamic, safety, tolerability, and immunogenicity profiles of AVT03 and Prolia® in healthy male subjects.

Ongoing studies:

AVT03-GL-C01

A randomised, double-blind, parallel design, repeat dose, 2-arm, multicenter study comparing the efficacy, safety, immunogenicity, and pharmacokinetic profiles of AVT03 and US-Prolia® in postmenopausal women with osteoporosis, ALVOBOND.

Table SIII.1: Cumulative subject exposure from clinical trials

Treatment	**Number of subjects**
AVT03	369
Comparator - Prolia®	369
Total subjects	**738**

Table SIII.2: Cumulative subject exposure to AVT03 from clinical trials by age

Age range	**Number of subjects**
0-28 years	0
28-50 years	103
More than 50 years	266
Total subjects	**369**

Table SIII.3: Cumulative subject exposure to AVT03 from clinical trials by Gender

Gender	**Number of subjects**
Male	103
Female	266
Total subjects	**369**

Table SIII.4: Cumulative subject exposure to AVT03 from clinical trials by race

Race	Number of subjects
Asian	3
Black or African American	116
Caucasian/White	284
Other	17
Unknown	0
Total subjects	**369**

Table SIII.5: Cumulative subject exposure to AVT03 from clinical trials by ethnicity

Ethnicity	Number of subjects*
Hispanic or Latino	3
Non-Hispanic or Latino	263
Total subjects	**266**

* No ethnicity data were collected in AVT03-GL-P01 study; the numbers are based on AVT03-GL-C01 study.

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

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

Osteonecrosis of jaw

Reason for exclusion: Patients with osteonecrosis of the jaw (ONJ) or risk factors for ONJ such as invasive dental procedures (e.g. tooth extraction, dental implants, oral surgery in the past 6 months), periodontal, and/or pre-existing dental disease requiring therapy should not use.

Is it considered to be included as missing information?: No

Rationale: Comprehensive wording concerning the osteonecrosis of the jaw associated with the use of denosumab is currently in section 4.4 "Special warnings and precautions for use" of the SmPC) and section 4.8 “Undesirable effects” of the SmPC.

Hypersensitivity to the active substance or any of the excipients

Reason for exclusion: Patients with known hypersensitivity to denosumab or excipients should not use.

Is it considered to be included as missing information?: No

Rationale: Use in this population is contraindicated in section 4.3 "Contraindications" and also comprehensive wording concerning the risk of hypersensitivity reaction is in section 4.8 “Undesirable effects” of the SmPC.

Atypical femoral fracture

Reason for exclusion: Patients with bone fractures, presence of active healing fractures, or recent bone fracture within 6 months prior to start of denosumab treatment should not use.

Is it considered to be included as missing information?: No

Rationale: Comprehensive wording concerning atypical femoral fracture associated with the use of denosumab is currently in section 4.4 "Special warnings and precautions for use" and section 4.8 “Undesirable effects” of the SmPC.

Hypocalcaemia

Reason for exclusion: Patients with abnormal serum calcium level should not use.

Is it considered to be included as missing information?: No

Rationale: Use in this group of patients is contraindicated in section 4.3 "Contraindications" and also comprehensive wording concerning the risk of hypocalcaemia (is currently in section 4.2 “Posology and method of administration”, section 4.4 "Special warnings and precautions for use" and section 4.8 “Undesirable effects” of the summary of product characteristics (SmPC).

Infection

Reason for exclusion: Patients with any current active infections, including localised infections, or any recent history (within 1 week prior to denosumab administration) of active infections, cough or fever or a history of recurrent or chronic infections (includes coronavirus disease 19) should not use.

Is it considered to be included as missing information?: No

Rationale: Comprehensive wording concerning the risk of infections after denosumab therapy is in section 4.8 “Undesirable effects” of the SmPC.

Malignancy

Reason for exclusion: Patients with history or presence of malignancy (except for successfully treated basal or squamous cell carcinoma) should not use.

Is it considered to be included as missing information?: Yes

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, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

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

Table SIV.2: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	

Type of special population	Exposure
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program
Population with relevant different ethnic origin	Not included in the clinical development program
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program
Other	Not included in the clinical development program

Part II: Module SV - Post-authorisation experience

Not applicable, since the RMP is prepared for initial marketing authorisation applicant (MAA), there is no post-authorisation data available for this product.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Denosumab is not structurally or pharmacologically related to any drug known to cause abuse or dependence, and it is not expected to have a potential for misuse as a recreational drug.

Part II: Module SVII - Identified and potential risks

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

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

Not all adverse reactions are necessarily considered a risk for the medicinal product in a given therapeutic context and not all risks qualify as important to be included in the list of safety concerns for the purpose of risk management planning.

The information available for denosumab has been analysed and those risks not considered important for inclusion in the list of safety concerns in the RMP (along with the reason of not inclusion) are detailed below:

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- Gastrointestinal disorders: Diarrhoea, Tooth extraction.
- Metabolism and nutrition disorders: Hypocalcaemia, Hypophosphatemia.

- Respiratory, thoracic and mediastinal disorders: Dyspnoea.
- Skin and subcutaneous tissue disorders: Hyperhidrosis, Lichenoid drug eruptions.

Known risks that do not impact the benefit-risk profile (in relation to the severity of the indication treated):

- Immune system disorders: Drug hypersensitivity.

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

- Immune system disorders: Anaphylactic reaction.

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

Important identified risk 1: Osteonecrosis of the jaw

Osteonecrosis of the Jaw have been observed in the clinical trial program of the originator. These cases have also been reported in post-marketing setting of the originator.

Risk-benefit impact:

Considering the safety measures described in the SmPC, it is expected that the risk-benefit balance of the product will be favourable.

Important identified risk 2: Atypical femoral fracture

Atypical femoral fracture cases have been observed in the clinical trial program of the originator. These cases have also been reported in post-marketing setting of the originator.

Risk-benefit impact:

Considering the safety measures described in the SmPC, it is expected that the risk-benefit balance of the product will be favourable.

Important identified risk 3: Hypercalcemia several months after the last dose in patients with giant cell tumour of bone and in patients with growing skeletons

This risk was identified in clinical trial program of the originator, of adolescent and adult patients with GCTB, and in post-marketing reports of paediatric patients using.

Risk-benefit impact:

Considering the safety measures described in the SmPC, it is expected that the risk-benefit balance of the product will be favourable.

Important potential risk 1: Cardiovascular events

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

Risk-benefit impact:

Since there is scarce experience with the use of denosumab and cardiovascular event, this use needs to be further studied.

Important potential risk 2: Malignancy

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

Risk-benefit impact:

Since there is scarce experience with the use of denosumab and malignancy, this use needs to be further studied.

Important potential risk 3: Delay in diagnosis of primary malignancy in giant cell tumour of bone

This is considered a potential risk based on theoretical concern which has not been substantiated in the extensive clinical study program or in the post-marketing experience of the originator.

Risk-benefit impact:

Since there is scarce experience with the use of denosumab and the risk, this use needs to be further studied.

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

This is considered a potential risk based on theoretical concern which has not been substantiated in the extensive clinical study program or in the post-marketing experience of the originator.

Risk-benefit impact:

Since there is scarce experience with the use of denosumab and the risk, this use needs to be further studied.

Missing information 1: Patients with prior intravenous bisphosphonate treatment

Insufficient data on efficacy and safety are available for this population group.

Risk-benefit impact:

Since there is scarce experience with the use of denosumab in patients with prior intravenous bisphosphonate treatment, this use needs to be further studied.

Missing information 2: 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

Insufficient data on efficacy and safety are available for this population group.

Risk-benefit impact:

Since there is scarce experience related to 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, this use needs to be further studied.

Missing information 3: Off-label use in patients with giant cell tumour of bone that is resectable where resection is unlikely to result in severe morbidity

Insufficient data on efficacy and safety are available for this population group.

Risk-benefit impact:

Since there is scarce experience related to off-label use in patients with giant cell tumour of bone that is resectable where resection is unlikely to result in severe morbidity, this use needs to be further studied.

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

Not applicable, as no European Union Risk Management Plan (EU-RMP) has previously been submitted.

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

Important identified risk 1: Osteonecrosis of the Jaw

Potential mechanisms: Osteonecrosis of the jaw (ONJ) appears to be multifactorial and multiple hypotheses have been postulated and have included factors such as inhibition of bone remodelling, infection and inflammation, inhibition of angiogenesis, soft tissue toxicity, altered immunity and genetic predisposition. As yet, evidence supporting these hypotheses has been variable and little is understood in how these multiple pathways might interact (Fassio, 2017; Aghaloo et al, 2015).

Evidence source(s) and strength of evidence: Osteonecrosis of the Jaw have been observed in the clinical trial program of the originator. These cases have also been reported in post-marketing setting of the originator.

Characterisation of the risk:

Frequency: In the pooled pivotal SRE Solid Tumour studies of the originator, 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 of the originator, 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. In Study 20101363 of the originator, 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 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 (Aimazrooa and Woo, J Amer Dental Assoc, 2009; 140:864-875; Estilo et al, J Clin Oncol, 2008; 26:4037-4038; Mehrotra and Ruggiero, Hematol, 2006; 2006:356-360; Ruggiero et al, J Oncol Pract, 2006; 2:7-14).

Preventability: A dental examination with appropriate preventive dentistry is recommended prior to treatment with originator-XGEVA, 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 XGEVA should receive care by a dentist or an oral surgeon. In patients who develop ONJ during treatment with XGEVA, 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 XGEVA 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 labeling and a patient reminder card that has been proposed to minimise 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.

Important identified risk 2: Atypical Femoral Fracture

Potential mechanisms: Prolonged suppression of bone turnover may be associated with increased risk of atypical femoral fracture (AFF), but the pathogenesis remains unclear and the causes of AFF are likely multi-factorial. Based on nonclinical studies of the originator, collagen cross-linking and maturation, accumulation of micro-damage and advanced glycation end products, mineralisation, remodelling, vascularity, and angiogenesis lend biologic plausibility to a potential association between these effects and AFF (Ismail et al, 2018; Shane et al, 2010).

Evidence source(s) and strength of evidence: Atypical femoral fracture cases have been observed in the clinical trial program of the originator. These cases have also been reported in post-marketing setting of the originator.

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 utilising monthly

dosing throughout [0.1 %, 6 subjects with AFF in 6101 subjects]). All 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 of the originator, AFF has been reported uncommonly in patients treated with originator-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 (Bubbear et al, 2016; Unnanuntana et al, 2013).

Risk factors and risk groups: Long-term anti resorptive treatment has been associated with AFF. Corticosteroids have also been reported in the literature to potentially be associated with AFF (Meier et al, Arch Intern Med, 2012; 172:930-936; Giusti et al, Bone, 2011; 48(5):966-971). Atypical femoral fractures have also been reported in patients with certain comorbid conditions (eg, vitamin D deficiency, rheumatoid arthritis [RA], hypophosphatasia) and with use of bisphosphonates, glucocorticoids, and proton pump inhibitors (Shane et al, J Bone Miner Res, 2010; 25:2267-2294).

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

Impact on the risk-benefit balance of the product: The risk of AFF events has been considered in the product benefit-risk assessment. In light of the product labelling that has been proposed to minimise 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.

Important identified risk 3: Hypercalcemia several months after the last dose in patients with giant cell tumour of bone and in patients with growing skeletons

Potential mechanisms: The mechanism(s) of hypercalcemia several months after the last dose of denosumab in patients with GCTB and in patients with a growing skeleton are not well characterised, but may be a consequence of the following, alone, or in combination:

Denosumab treatment and resultant RANK/RANKL pathway inhibition in adults with giant-cell containing lesions such as GCTB leads to histopathologic evidence of a dramatic decrease in osteoclast-like giant cells which is complemented by woven bone formation and calcification within the tumours and even at sites of distant metastases (Ghermandi et al, 2016; Yamagishi et al, 2016; Branstetter et al, 2012). It is possible this calcium could serve as a depot that is mobilised

with reactivation of tumour-associated, RANKL driven giant cell mediated osteolysis following cessation of XGEVA.

- 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 tumours themselves that have partially ossified in the cases of the adult patients with tumour recurrence via an autocrine/paracrine mechanism (Cowan et al, 2011).
- The magnitude of the resorptive response following treatment withdrawal in the patients with GCTB and in those with an immature skeleton could be dictated by the normal high rate of bone turnover within the GCTB lesion or in the growing 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 intratumour signalling pathways (eg, parathyroid hormone-related protein) in GCTB.

Evidence source(s) and strength of evidence: This risk was identified in clinical trial program of the originator, of adolescent and adult patients with GCTB, and in post-marketing reports of paediatric patients using.

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 of the originator 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 of the originator, the events of hypercalcemia in the 4 subjects from Study 20062004 of the originator were considered grade 2, 3, or 4 in severity. All subjects had acute renal injury and all were hospitalised. Three of 4 subjects had more than 1 event. The severity of the events in the post marketing 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. Patients may present with severe hypercalcemia requiring hospitalisation.

Impact on the risk-benefit balance of the product: 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 XGEVA. In general, the most common cause of hypercalcemia in humans is hyperparathyroidism, particularly among women and individuals aged 65 years or older (Minisola et al, BMJ, 2015;350:h2723). 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 (Machado et al, J Clin Med, 2015; 4:414-424; Minisola et al, BMJ, 2015;350:h2723).

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 minimise 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.

Important potential risk 1: Cardiovascular events

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

Evidence source(s) and strength of evidence: This is a theoretical risk based on epidemiological data demonstrating elevated osteoprotegerin in patients with cardiovascular disease.

Characterisation of the risk:

Frequency: In the pooled pivotal SRE Solid Tumour studies, subject incidence of cardiovascular (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 of the originator with denosumab 120 mg Q4W in subjects with castrate-resistant prostate cancer (CRPC) (Study 20050147), 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 of the originator, 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 hospitalised for treatment and disability may occur.

Risk factors and risk groups: The denosumab development program comprises studies of older subject populations (eg, 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 (Schulz et al, J Clin Endocrinol Metab, 2004; 89:4246-4253; Hak et al, Arlerioscler Thromb Vase Bioi, 2000; 20:1926-1931). 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 (Murphy and Dargie, Drug Safety, 2007; 30(9):783-804; Smith et al, Circulation, 2004; 1 09(21):2613-2616).

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 of the originator in the advanced cancer and postmenopausal osteoporosis (PMO)/hormone ablation therapy (HALT) settings.

Important potential risk 2: Malignancy

Potential mechanisms: The risk of malignancy is a theoretical concern that RANKL inhibition may lead to an increased risk for a new primary malignancy (NPM) by impairing immune surveillance mechanisms.

Evidence source(s) and strength of evidence: This is considered a potential risk based on theoretical concerns and has not been substantiated in the extensive clinical study program or in the post-marketing experience of the originator.

Characterisation of the risk:

Frequency: In the primary, double-blind treatment phases of 4 phase 3 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 of the originator, 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 of the originator 20062004 in GCTB, 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 I, 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 of the originator, 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 1 000 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 1 000 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 recognised 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 minimise 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/HAL T and advanced cancer settings.

Important potential risk 3: Delay in diagnosis of primary malignancy in giant cell tumour of bone

Potential mechanisms: Due to well described sampling error at the time of GCTB diagnosis, primary malignancy in giant cell tumour of bone (PMGCTB) may be missed and benign GCTB may be presumed. Based on the mechanism of action and pathology of GCTB, denosumab is only expected to treat benign GCTB. However, there was a theoretical concern that treatment of an undiagnosed PMGCTB with denosumab could delay the diagnosis of PMGCTB.

Evidence source(s) and strength of evidence: This is considered a potential risk based on theoretical concern which has not been substantiated in the extensive clinical study program or in the post-marketing experience of the originator.

Characterisation of the risk: In clinical studies of the originator in GCTB, based on medical review, 11 subjects (2.1 %; N = 523) had GCTB bone malignancies. Of these, 5 subjects (1.0%) had PMGCTB.

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 minimise 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.

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

Potential mechanisms: The pathogenesis of hypercalcemia several months after the last dose in patients other than those with GCTB or growing skeletons may be a consequence of the transient increase in bone turnover activity. Upon cessation of denosumab, the disinhibition of RANKL allows for terminal differentiation and activation of osteoclasts, which were suppressed during treatment. In patients with underlying causes for calcium dyscrasias (ie, subclinical hyperparathyroidism), denosumab discontinuation, with its transient increase in bone 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: This is considered a potential risk based on theoretical concern which has not been substantiated in the extensive clinical study program or in the post-marketing experience of the originator.

Characterisation of the risk: Cases of hypercalcemia in the off treatment period have been reported in clinical studies of the originator, 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 hospitalisation. Patients who experience hypercalcemia may develop complications such as acute renal injury.

Risk factors and risk groups: Patients other than those with GCTB or growing skeletons following cessation of denosumab.

Preventability: No preventive measures are known.

Impact on the risk-benefit balance of the product: The risk of hypercalcemia events following treatment discontinuation in patients other than those with GCTB or growing skeletons has been incorporated in the product benefit-risk assessment, and the overall benefit-risk balance remains positive.

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

Missing information 1: Patients with prior intravenous bisphosphonate treatment

Evidence source: Insufficient data on efficacy and safety are available for this population group.

Population in need of further characterisation: Since there is scarce experience with the use of denosumab in patients with prior intravenous bisphosphonate treatment, this use needs to be further studied.

Missing information 2: Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumour of bone

Evidence source: Insufficient data on efficacy and safety are available for this population group.

Population in need of further characterisation: Since there is scarce experience related to 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, this use needs to be further studied.

Missing information 3: Off-label use in patients with giant cell tumour of bone that is resectable where resection is unlikely to result in severe morbidity

Evidence source: Insufficient data on efficacy and safety are available for this population group.

Population in need of further characterisation: Since there is scarce experience related to off-label use in patients with giant cell tumour of bone that is resectable where resection is unlikely to result in severe morbidity, this use needs to be further studied.

Part II: Module SVIII - Summary of the safety concerns

The summary of safety concerns for Denosumab is based on the EU-RMP for XGEVA® (Originator) version 36.0 dated 04 September 2024 published on the European Medicines Agency (EMA) website.

Consequently, the summary of safety concerns for Denosumab is the following:

Table SVIII.1: 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 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

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities include routine follow-up of all adverse drug reaction reports lacking information on the batch number and/or brand name. Therefore, all appropriate measures

are taken for biological medicinal products to clearly identify the names of the products and batch numbers.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific Adverse Reaction Follow-up Questionnaires

In order to optimize the data collection for defined medical conditions, specific adverse reaction follow-up questionnaires will be used for:

- Osteonecrosis of the jaw
- Potential Atypical fracture

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 XGEVA in the post marketing environment.
Potential atypical fracture	Atypical femoral fracture	To monitor the reporting rate and nature of AFF in patients treated with XGEVA in the post marketing environment.

The forms are provided in the **Annex 4** of the RMP.

Other Forms of Routine Pharmacovigilance Activities for safety concerns

No other forms of Routine Pharmacovigilance Activities beyond adverse reaction reporting, signal detection and the ones described above will be implemented for Denosumab.

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities will be conducted.

III.3 Summary Table of additional Pharmacovigilance activities

No additional pharmacovigilance activities will be conducted.

Part IV: Plans for post-authorisation efficacy studies

Not applicable as no post-authorisation efficacy studies are planned.

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

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Osteonecrosis of the jaw	Routine risk communication: SmPC sections 4.3, 4.4, 4.8 and 5.1. Patient Information Leaflet (PIL) sections 2 and 4. Routine risk minimisation 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 SmPC Section 4.4. In order to inform patients of this risk, corresponding text is also present in the PIL sections 2 and 4. Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription.
Atypical femoral fracture	Routine risk communication: SmPC sections 4.4 and 4.8. PIL sections 2 and 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation for reporting new or unusual thigh, hip, or groin pain is included in SmPC Section 4.4. In order to inform patients of this risk, corresponding text is also present in the PIL sections 2 and 4. Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription.
Hypercalcemia several months after the last dose in patients with giant cell tumour of bone and in patients with growing skeletons	Routine risk communication: SmPC sections 4.4 and 4.8. PIL sections 2 and 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendations for monitoring the patients for signs and symptoms of hypercalcaemia after discontinuation of denosumab treatment are included in SmPC Section 4.4.

	In order to inform patients of this risk, corresponding text is also present in the PIL sections 2 and 4. Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription.
Cardiovascular events	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription.
Malignancy	Routine risk communication: SmPC sections 4.4, 4.8 and 5.1. PIL section 4. Routine risk minimisation 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 SmPC Section 4.4. In order to inform patients of this risk, corresponding text is also present in the PIL section 4. Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription.
Delay in diagnosis of primary malignancy in giant cell tumour of bone	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription.
Hypercalcemia several months after the last	Routine risk communication:

dose in patients other than those with giant cell tumour of bone or growing skeletons	None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription.
Patients with prior intravenous bisphosphonate treatment	Routine risk communication: SmPC sections 4.5 and 5.1. PIL section 2. Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription.
Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumour of bone	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription.
Off-label use in patients with giant cell tumour of bone that is resectable where resection is unlikely to result in severe morbidity	Routine risk communication: SmPC section 5.1. Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription.

V.2. Additional Risk Minimisation Measures

Additional risk minimisation measures are in place for the following safety concern:

- Osteonecrosis of the jaw

Patient reminder card

Objectives	Patient reminder cards will be distributed to address the following risk: • Osteonecrosis of the jaw
Rationale for the additional risk minimisation 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 injections for osteoporosis and bone loss, including: • to tell their doctors/nurses if they have any problems with their mouth or teeth before starting treatment; • to maintain good oral hygiene and receive routine dental check-ups during treatment; • to inform their doctor and teel their dentist that they are being treated with Denosumab if they are under dental treatment or will undergo dental surgery; • to contact their doctor and dentist immediately if they experience any problems with their mouth or teeth such as loose teeth, pain or swelling, nonhealing of sores, or discharge.
Target audience and planned distribution path	Target audience will be the patients. The patient reminder card will be distribution method will be agreed with each national authority before launching the product in respective countries.
Plans to evaluate the effectiveness of the interventions and criteria for success	Reported cases will be monitored to observe the decreased frequency of occurrence of osteonecrosis of Jaw before and after introduction of reminder card compared with rest of the world. In addition the focused questionnaire for post marketing reports of ONJ presented in Annex4, 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 risk minimisation activities	No change in risk-benefit profile

V.3 Summary of risk minimisation measures

Safety concern	Routine risk minimisation activities	Pharmacovigilance activities
Osteonecrosis of the jaw	Routine risk minimisation measures: SmPC sections 4.3, 4.4, 4.8 and 5.1. PIL sections 2 and 4. 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 SmPC Section 4.4. In order to inform patients of this risk, corresponding text is also present in the PIL sections 2 and 4. Legal status: Restricted medical prescription. Additional risk minimisation measures: Patient reminder card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific follow-up questionnaire. Additional pharmacovigilance activities: None.
Atypical femoral fracture	Routine risk minimisation measures: SmPC sections 4.4 and 4.8. PIL sections 2 and 4. Recommendation for reporting new or unusual thigh, hip, or groin pain is included in SmPC Section 4.4. In order to inform patients of this risk, corresponding text is	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific follow-up questionnaire Additional pharmacovigilance activities: None.

Safety concern	Routine risk minimisation activities	Pharmacovigilance activities
	also present in the PIL sections 2 and 4. Legal status: Restricted medical prescription. Additional risk minimisation measures: 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 and 4.8. PIL sections 2 and 4. Recommendations for monitoring the patients for signs and symptoms of hypercalcaemia after discontinuation of denosumab treatment are included in SmPC Section 4.4. In order to inform patients of this risk, corresponding text is also present in the PIL sections 2 and 4. Legal status: Restricted medical prescription. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Cardiovascular events	Routine risk minimisation measures: None. Legal status: Restricted medical prescription. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

Safety concern	Routine risk minimisation activities	Pharmacovigilance activities
Malignancy	Routine risk minimisation measures: SmPC sections 4.4, 4.8 and 5.1. PIL section 4. Recommendations for monitoring the patients for radiological signs of malignancy, new malignancy, or osteolysis are included in SmPC Section 4.4. In order to inform patients of this risk, corresponding text is also present in the PIL section 4. Legal status: Restricted medical prescription. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Delay in diagnosis of primary malignancy in giant cell tumour of bone	Routine risk minimisation measures: None. Legal status: Restricted medical prescription. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Hypercalcemia several months after the last dose in patients other than those with giant cell tumour of bone or growing skeletons	Routine risk minimisation measures: None. Legal status: Restricted medical prescription. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

Safety concern	Routine risk minimisation activities	Pharmacovigilance activities
Patients with prior intravenous bisphosphonate treatment	Routine risk minimisation measures: SmPC sections 4.5 and 5.1. PIL section 2. Legal status: Restricted medical prescription. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumour of bone	Routine risk minimisation measures: None. Legal status: Restricted medical prescription. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Off-label use in patients with giant cell tumour of bone that is resectable where resection is unlikely to result in severe morbidity	Routine risk minimisation measures: SmPC section 5.1. Legal status: Restricted medical prescription. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

Part VI: Summary of the risk management plan

Summary of risk management plan for Xbonzy 120 mg solution for injection (Denosumab)

This is a summary of the risk management plan (RMP) for Xbonzy 120 mg solution for injection (Hereinafter referred to as “Denosumab”). The RMP details important risks of Denosumab, how these risks can be minimised, and how more information will be obtained about Denosumab's risks and uncertainties (missing information).

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

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

I. The medicine and what it is used for

Denosumab 120 mg solution for injection is indicated 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 in the 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 the subcutaneous route of administration.

Further information about the evaluation of Denosumab’s benefits can be found in Denosumab’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage: link to the EPAR summary landing page will be updated post authorisation.

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

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

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

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

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

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

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including 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 Denosumab is not yet available, it is listed under 'missing information' below

II.A List of important risks and missing information

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

List of important risks and missing information	
Important identified risks	• Osteonecrosis of the jaw • 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

II.B Summary of important risks

Important identified risk: Osteonecrosis of the jaw	
Evidence for linking the risk to the medicine	Osteonecrosis of the Jaw have been observed in the clinical trial program of the originator. These cases have also been reported in post-marketing setting of the originator.
Risk factors and risk groups	Risk factors associated with ONJ include the use of antiresorptives (particularly aminobisphosphonates delivered by intravenous [IV] dosing), older age, poor dental hygiene,

Important identified risk: Osteonecrosis of the jaw	
	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 (Aimazrooa and Woo, J Amer Dental Assoc, 2009; 140:864-875; Estilo et al, J Clin Oncol, 2008; 26:4037-4038; Mehrotra and Ruggiero, Hematol, 2006; 2006:356-360; Ruggiero et al, J Oncol Pract, 2006; 2:7-14).
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.3, 4.4, 4.8 and 5.1. Patient Information Leaflet (PIL) sections 2 and 4. 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 SmPC Section 4.4. In order to inform patients of this risk, corresponding text is also present in the PIL sections 2 and 4. Legal status: Restricted medical prescription. Additional risk minimisation measures: Patient reminder card.

Important identified risk: Atypical femoral fracture	
Evidence for linking the risk to the medicine	Atypical femoral fracture cases have been observed in the clinical trial program of the originator. These cases have also been reported in post-marketing setting of the originator.
Risk factors and risk groups	Long-term anti resorptive treatment has been associated with AFF. Corticosteroids have also been reported in the literature to potentially be associated with AFF (Meier et al, Arch Intern Med, 2012; 172:930-936; Giusti et al, Bone, 2011; 48(5):966-971). Atypical femoral fractures have also been reported in patients with certain comorbid conditions (eg, vitamin D deficiency, rheumatoid arthritis [RA], hypophosphatasia) and with use of bisphosphonates, glucocorticoids, and proton pump inhibitors (Shane et al, J Bone Miner Res, 2010; 25:2267-2294).

Important identified risk: Atypical femoral fracture	
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4 and 4.8. PIL sections 2 and 4. Recommendation for reporting new or unusual thigh, hip, or groin pain is included in SmPC Section 4.4. In order to inform patients of this risk, corresponding text is also present in the PIL sections 2 and 4. Legal status: Restricted medical prescription. Additional risk minimisation measures: None.

Important identified risk: Hypercalcemia several months after the last dose in patients with giant cell tumour of bone and in patients with growing skeletons	
Evidence for linking the risk to the medicine	This risk was identified in clinical trial program of the originator, of adolescent and adult patients with GCTB, and in post-marketing reports of paediatric patients using.
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 (Minisola et al, BMJ, 2015;350:h2723). 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 (Machado et al, J Clin Med, 2015; 4:414-424; Minisola et al, BMJ, 2015;350:h2723).
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4 and 4.8. PIL sections 2 and 4. Recommendations for monitoring the patients for signs and symptoms of hypercalcaemia after discontinuation of denosumab treatment are included in SmPC Section 4.4. In order to inform patients of this risk, corresponding text is also present in the PIL sections 2 and 4. Legal status: Restricted medical prescription.

Important identified risk: Hypercalcemia several months after the last dose in patients with giant cell tumour of bone and in patients with growing skeletons	
	Additional risk minimisation measures: None.

Important potential risk: Cardiovascular events	
Evidence for linking the risk to the medicine	This is a theoretical risk based on epidemiological data demonstrating elevated osteoprotegerin in patients with cardiovascular disease.
Risk factors and risk groups	The denosumab development program comprises studies of older subject populations (eg, 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 (Schulz et al, J Clin Endocrinol Metab, 2004; 89:4246-4253; Hak et al, Arlerioscler Thromb Vase Bioi, 2000; 20:1926-1931). 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 (Murphy and Dargie, Drug Safety, 2007; 30(9):783-804; Smith et al, Circulation, 2004; 1 09(21):2613-2616).
Risk minimisation measures	Routine risk minimisation measures: None. Legal status: Restricted medical prescription. Additional risk minimisation measures: None.

Important potential risk: Malignancy	
Evidence for linking the risk to the medicine	This is considered a potential risk based on theoretical concerns and has not been substantiated in the extensive clinical study program or in the post-marketing experience of the originator.
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.

Important potential risk: Malignancy	
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4, 4.8 and 5.1. PIL section 4. Recommendations for monitoring the patients for radiological signs of malignancy, new malignancy, or osteolysis are included in SmPC Section 4.4. In order to inform patients of this risk, corresponding text is also present in the PIL section 4. Legal status: Restricted medical prescription. Additional risk minimisation measures: None.

Important potential risk: Delay in diagnosis of primary malignancy in giant cell tumour of bone	
Evidence for linking the risk to the medicine	This is considered a potential risk based on theoretical concern which has not been substantiated in the extensive clinical study program or in the post-marketing experience of the originator.
Risk factors and risk groups	Patients with GCTB are known to be at risk for PMGCTB.
Risk minimisation measures	Routine risk minimisation measures: None. Legal status: Restricted medical prescription. Additional risk minimisation measures: None.

Important potential risk: Hypercalcemia several months after the last dose in patients other than those with giant cell tumour of bone or growing skeletons	
Evidence for linking the risk to the medicine	This is considered a potential risk based on theoretical concern which has not been substantiated in the extensive clinical study program or in the post-marketing experience of the originator.
Risk factors and risk groups	Patients other than those with GCTB or growing skeletons following cessation of denosumab.

Important potential risk: Hypercalcemia several months after the last dose in patients other than those with giant cell tumour of bone or growing skeletons	
Risk minimisation measures	Routine risk minimisation measures: None. Legal status: Restricted medical prescription. Additional risk minimisation measures: None.

Missing information: Patients with prior intravenous bisphosphonate treatment	
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.5 and 5.1. PIL section 2. Legal status: Restricted medical prescription. Additional risk minimisation measures: None.

Missing information: Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumour of bone	
Risk minimisation measures	Routine risk minimisation measures: None. Legal status: Restricted medical prescription. Additional risk minimisation 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 minimisation measures: None. Legal status: Restricted medical prescription. Additional risk minimisation measures: None.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

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

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

There are no studies required for Denosumab.

Part VII: Annexes

Table of contents

Annex 1 – EudraVigilance Interface

Not applicable.

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

Not applicable.

Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

Not applicable.

Annex 4 - Specific adverse drug reaction follow-up forms

In order to optimize the data collection for defined medical conditions, specific follow-up questionnaires will be used:

- Osteonecrosis of the jaw
- Potential Atypical fracture

Follow-up Form Title	Version Number	Date of Follow-up version
Osteonecrosis of the jaw	1.0	September 2024
Potential atypical fracture	1.0	September 2024

DENOSUMAB - Specific Adverse Reaction Follow-up Questionnaire
Osteonecrosis of the Jaw

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

Patient Identifier | Patient | Date of Event Onset | Date of This

Gender: ☐ Male ☐ Female Weight:_____lb _____kg

Age at time of event: _____

Event Reported Term

Study No.

Safety Database No.

☐ Clinical Trial

☐ Post-marketing

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

Denosumab Indication

☐ Postmenopausal osteoporosis

☐ Bone loss from hormone ablation therapy

Please specify diagnosis_____

_____

☐ Advanced cancer with bone metastasis

Please specify cancer_____

☐ Other Please specify_____

_____

☐ Don't know

Denosumab Dose

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

☐ Other (Please specify)_____ _____s

☐ 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 the event

_____

DENOSUMAB - Specific Adverse Reaction Follow-up Questionnaire

Osteonecrosis of the Jaw (Continued)

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 visualised/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_____

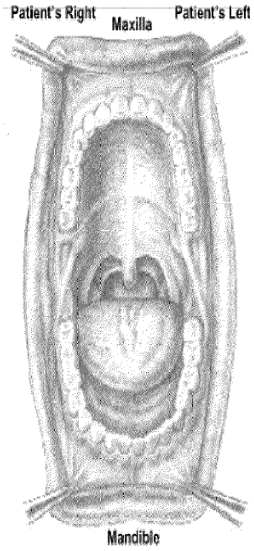
Prior history of metastatic disease to jaw:

☐ 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)

_____

Report to
Email:

Oral Findings

Evidence of infection: ☐ No ☐ Yes ☐ Unknown

Please describe _____

Exposed bone at the site of extraction

☐ No ☐ Yes ☐ Unknown

Complete coverage of involved area(s) by mucosa

☐ No ☐ Yes ☐ Unknown

If yes, date of complete mucosal coverage _____

Clinical Symptoms (Please indicate dates as DD/MM/YYYY)

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

_

Please describe the clinical signs/symptoms/location:

_____

___

_____

___

_____

___

_____

___

REPORTER

Name:

Address:

City: State/

Country: Province:

Email: Postal code:

Phone (include country code)

Signature _____

Title _____ **Date** _____

DENOSUMAB - Specific Adverse Reaction Follow-up Questionnaire

Osteonecrosis of the Jaw (Continued)

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 of examination _____

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

TREATMENT INFORMATION (Please indicate what treatments were administered 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 the treatment_____

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

Please describe outcomes of the treatment_____

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

Start Date _____ Stop Date_____

Please describe outcomes of the 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 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)/

Start date _____ Stop date _____

OTHE HISTORY (Please indicate 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 number of drinks per week _____

Diabetes ☐ No ☐ Yes ☐ Unknown

If yes, ☐ Type I ☐ Type II

Report to

Email:

REPORTER

Name:

Address:

City: State/

Country: Province:

Email: Postal code:

Phone (include country code)

Signature _____

Title _____ **Date** _____

DENOSUMAB - Specific Adverse Reaction Follow-up Questionnaire
Potential Atypical Fracture

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

Patient Identifier | Patient | Date of Event Onset | Date of This

Gender: ☐ Male ☐ Female Weight:_____lb _____kg

Age at time of event: _____

Study Number (If applicable)

Event

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

Denosumab Indication

☐ Postmenopausal osteoporosis

☐ Bone loss from hormone ablation therapy

Please specify diagnosis_____

☐ Advanced cancer with bone metastasis

Please specify cancer_____

☐ Other (Please specify)_____

☐ Don't know

Denosumab Dose

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

☐ Other (Please specify)_____

☐ Don't know

Denosumab Exposure

Denosumab first administered (date)
_____

Last denosumab dose before event (date)
_____

Doses of denosumab were skipped

☐ Yes ☐ No ☐ Unknown

If yes, please specify
_____

Doses of denosumab given after event began

☐ Yes ☐ No ☐ Unknown

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

DIAGNOSIS (Check all that apply)

Location of fracture:
☐ Femur neck

☐ Femur distal

☐ Femur midshaft

☐ Femur intertrochanter

☐ Femur subtrochanter

☐ Other location (specify): _____

Diagnostic imaging used to confirm fracture:

☐ X-ray ☐ CT-Scan ☐ MRI

Type of trauma reported at time of fracture:
☐ No Trauma

☐ Fall from standing height or less

☐ Fall on stairs, steps or curbs

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

☐ Minimal trauma other than a fall

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

☐ Severe trauma other than a fall (e.g., car accident)

DIAGNOSIS (Check all that apply)

Date of imaging at the time of femur fracture (DD/MM/YYYY) _____

☐ 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 proximal femoral shaft:

☐ Yes ☐ No ☐ Not reported

☐ Unknown type of trauma

Early symptom of pain over fracture site:

☐ Pain at site at rest

☐ Pain at site with weight bearing

☐ None

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

If yes:

☐ Date of fracture union (DD/MM/YYYY): _____

☐ Patient able to walk without assistance:

☐ Yes ☐ No ☐ Unknown

☐ Fracture union confirmed through imaging:

☐ Yes ☐ No ☐ Unknown

If yes, check all diagnostic imaging that apply:

☐X-ray ☐CT-Scan ☐MRI

DENOSUMAB - Specific Adverse Reaction Follow-up Questionnaire
Potential Atypical Fracture (Continued)

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

Patient Identifier	Patient Initials	Date of This Report

TREATMENT (Please provide dates and indicate attachments if available)

Methods to reduce and set fracture:

☐ Non-surgical reduction_____

☐ Casting_____

☐ Surgery _____

☐ Revision surgery (2nd surgery) _____

☐ Other_____

_____

☐ Unknown_____

_____

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

General:

☐ History or current corticosteroid use

☐ Affected hip with prior surgical pinning

☐ Affected hip with prior hip replacement

Cancer:

Evidence of any metastases: ☐Yes ☐No ☐Unknown

If yes, did metastases 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:

_____

_____

REPORTER

Name:

Address:

City: State/

Country: Province:

Email: Postal code:

Phone (include country code)

Signature

_____

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

Copies of records/consults/radiology report attached

☐Yes ☐ No

Report to

Email:

Title _____ **Date** _____

Annex 5 - Protocols for proposed and on-going studies in RMP part IV

Not applicable.

Annex 6 - Details of proposed additional risk minimisation activities

Approved key messages of the additional risk minimisation measures

Physician educational material

- **Patient card**
- **Patient reminder card:**

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

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

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

Annex 7 - Other supporting data (including referenced material)

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Xgeva (Denosumab) 120 mg version 36.0 dated 04 September 2024

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Annex 8 – Summary of changes to the risk management plan over time

Version	Approval date Procedure	Change
0.1	Not applicable H0006552	New application
0.2	Not applicable EMEA/H/C/006722/0000	In response to Day 120 Assessor comments, the following sections are updated • Part I: Product(s) Overview: Marketing authorisation procedure is updated from H0006552 to EMEA/H/C/006722/0000 • Part II: Module SVIII - Summary of the safety concerns is updated - The following Important potential risks are deleted • Infection • Osteonecrosis outside the jaw including external auditory canal – The missing information “Immunogenicity following a significant change to the manufacturing process“ is deleted. • In Part II: SVII-1.2, SVII.3.1, SVII.3., information related to deleted safety concerns "Infection", "Osteonecrosis outside the jaw including external auditory canal" and “Immunogenicity following a significant change to the manufacturing process“ is removed. • Part III.1 Routine pharmacovigilance activity of specific adverse reaction follow-up questionnaire related to infection is removed. • Part V.1 and V.3: Risk minimisation measures and additional risk minimisation measures related to deleted safety concerns "Infection", "Osteonecrosis outside the jaw including external auditory canal" and “Immunogenicity following a significant change to the manufacturing process“ are removed. Part VI: IIA - The following Important potential risks are deleted

Version	Approval date Procedure	Change
		• Infection • Osteonecrosis outside the jaw including external auditory canal – The missing information “Immunogenicity following a significant change to the manufacturing process“ is deleted. • In Part VI: IIB summary of important risks related to deleted safety concerns "Infection", "Osteonecrosis outside the jaw including external auditory canal" and “Immunogenicity following a significant change to the manufacturing process“ is removed. • Annex 4 is updated to remove specific adverse reaction follow-up questionnaire of infection. • Annex 6 is updated inline with reference product RMP.
0.3	Not applicable EMEA/H/C/006722/0000	Response to Day 150 and 180 assessor comments Following changes made: Part VI: II.A List of important risks and missing information – The important potential risk of “Osteonecrosis outside the jaw including external auditory canal” is removed from the table in Part VI: IIA
0.4	Not applicable EMEA/H/C/006722/0000	Following changes made: Invented name in the EEA updated – Xbonzy 120 mg solution for injection