EU Risk Management Plan for Acvybra 60 mg solution for injection in pre-filled syringe (Denosumab)

RMP version to be assessed as part of this application:

RMP Version number:	0.2
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 and procedure number updated
Summary of significant changes in this RMP:	Following changes made: Invented name in the European Economic Area (EEA) and procedure number updated – "Acvybra 60 mg solution for injection in pre-filled syringe" – Centralised (EMEA/H/C/006734/0000)
Other RMP versions under evaluation:	Not applicable
Details of the currently approved RMP:	Not applicable

QPPV name: [redacted]

QPPV signature:

Signed by: [redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
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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)	Drugs for treatment of bone diseases – Other drugs affecting bone structure and mineralisation ATC code: M05BX04
Marketing Authorisation Holder	Reddy Holding GmbH Kobelweg 95 Augsburg 86156 Germany
Medicinal products to which this Risk Management Plan (RMP) refers	01.
Invented name(s) in the European Economic Area (EEA)	Proposed: Acvybra 60 mg solution for injection in pre-filled syringe (Hereafter referred to as Denosumab)
Marketing authorisation procedure	Centralised: EMEA/H/C/006734/0000
Brief description of the product	Denosumab is a fully human monoclonal antibody of the immunoglobulin G (IgG) 2 subclass.
	Summary of mode of action Denosumab is a human monoclonal antibody (IgG2) that targets and binds with high affinity and specificity to Receptor activator of nuclear factor kappa-B ligand (RANKL), denosumab is a human monoclonal antibody (IgG2) that targets and binds with high affinity and specificity to RANKL, Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function and survival, thereby decreasing bone resorption in cortical and trabecular bone.
	Important information about its composition Denosumab is a human monoclonal IgG2 antibody produced in a mammalian cell line (Chinese hamster ovary cells) by recombinant deoxyribonucleic acid technology.

Hyperlink to the Product Information	Please refer to CTD Module 1.3.1
Indication(s) in the EEA	Current: Denosumab 60 mg solution for injection in pre-filled syringe is indicated for the treatment of: – osteoporosis in postmenopausal women and in men at increased risk of fractures. In postmenopausal women denosumab significantly reduces the risk of vertebral, non-vertebral and hip fractures. – bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. In men with prostate cancer receiving hormone ablation, denosumab significantly reduces the risk of vertebral fractures. – bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture.
	Proposed (if applicable): Not applicable.
Dosage in the EEA	Current: The recommended dose is 60 mg denosumab administered as a single subcutaneous injection once every 6 months into the thigh, abdomen or upper arm. Patients must be adequately supplemented with calcium and vitamin D.
	Proposed (if applicable): Not applicable.
Pharmaceutical form(s) and strengths	Current (if applicable): Solution for injection. Each pre-filled syringe contains 60 mg of denosumab in 1 mL of solution (60 mg/mL).
	Proposed (if applicable): Not applicable.
Is/will the product be subject to additional monitoring in the European Union (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 United States-licensed Prolia® and to EU-approved Prolia® (the originator).

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

Key safety findings from non-clinical studies and relevance to human usage [Prolia®, 2023]**:**

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Reproductive toxicity	At area under the curve (AUC) exposures up to 100-fold higher than the human exposure (every 6 months [Q6M]), denosumab showed no evidence of impaired fertility in cynomolgus monkeys during the non-clinical development program conducted originator. In a study of cynomolgus monkeys dosed with denosumab during the period equivalent to the first trimester at AUC exposures up to 99-fold higher than the human dose (Q6M), there was no evidence of maternal or fetal harm. In this study, fetal lymph nodes were not examined. In cynomolgus monkeys dosed with denosumab throughout pregnancy, effects including stillbirths and increased postnatal mortality; abnormal bone growth, reduced hematopoiesis, and tooth malalignment; absence of peripheral lymph nodes; and decreased neonatal growth were noted at AUC exposures up to 119-fold higher than the human exposure (60 mg Q6M). There was no evidence of maternal harm prior to labor; adverse maternal effects occurred infrequently during labor. Maternal mammary gland development was normal. In genetically engineered mice in which RANKL has been turned off by gene removal (a "knockout mouse"), studies suggest absence of RANKL during pregnancy may interfere with maturation	Monkeys exposed to denosumab in utero phenotypically resembled human infants with osteoclast-poor osteopetrosis due to inactivating mutations of RANK or RANKL. Therefore, denosumab is not recommended for use in pregnant women. Women should be advised not to become pregnant during and for at least 5 months after treatment with denosumab. It is not known if denosumab is excreted in human milk. Because denosumab has the potential to cause adverse reactions in nursing infants, a decision should be made on whether to discontinue nursing or discontinue the drug. Use in pregnant and lactating women is not considered a safety concern in this RMP. These populations are not included in the intended indications. In addition, risk minimisation via product labelling to avoid pregnancy and breastfeeding is in place.

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
	of the mammary gland leading to impaired lactation post-partum.	
Developmental toxicity	In neonatal rats, administration of the RANKL inhibitor osteoprotegerin (OPG) bound to Fc (OPG-Fc) resulted in reduced weight gain, reduced bone growth, and inhibited tooth eruption. Despite reductions in bone growth, most bone strength parameters were increased with these treatments. In neonatal cynomolgus monkeys exposed in utero to 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 generally returned to normal; there were no adverse effects on tooth eruption; and minimal to moderate mineralisation in multiple tissues was seen in 1 recovery animal. Adolescent cynomolgus monkeys who received doses of denosumab 150 times the expected clinical exposure had enlargement of epiphyseal growth plates with decreased removal of cartilage matrix in this area, considered to be consistent with the pharmacological activity of denosumab.	Treatment with denosumab may inhibit eruption of dentition in paediatric patients and may impair bone growth in paediatric patients with open growth plates. Denosumab is not approved for use in paediatric patients and should not be used in paediatric patients. Risk minimisation is in place via product labeling with respect to use in paediatric patients.

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 study:

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 Study:

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

Important Exclusion Criteria in Pivotal Studies Across the Development Program

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).

Skin infection leading to hospitalisation

Reason for exclusion: Patients having skin allergies, or are susceptible to auto-inflammatory skin disorders, or prone to the development of allergic skin inflammation should not use.

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

Rationale: Comprehensive wording concerning the development of a skin infections (predominantly cellulitis) after denosumab therapy is currently in section 4.4 "Special warnings and precautions for use" of the SmPC) and section 4.8 “Undesirable effects” of the SmPC.

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 ONJ 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 (AFF) 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.

Fracture healing complications

Reason for exclusion: criterion to avoid a potential safety bias.

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

Rationale: Comprehensive wording concerning fracture healing complications associated with the use of denosumab is currently in section 5.3 "Preclinical safety data" of the 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

SV.1 Post-authorisation exposure

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: Constipation, Abdominal discomfort.
- Musculoskeletal and connective tissue disorders: Pain in extremity, Musculoskeletal pain.
- Nervous system disorders: Sciatica.
- Skin and subcutaneous tissue disorders: Rash, Eczema, Alopecia, Lichenoid drug eruptions.

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.
- Musculoskeletal and connective tissue disorders: Osteonecrosis of the external auditory canal.

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

Important Identified Risk 1: Hypocalcaemia

Hypocalcaemia cases have been observed in the clinical trial program 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: Skin infection leading to hospitalisation

Cases of skin infection leading to hospitalisation have been observed in the clinical trial program 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: Osteonecrosis of the Jaw

Osteonecrosis of the Jaw have been observed in the clinical trial program 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 4: Hypersensitivity reactions

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

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 5: Atypical femoral fracture

Atypical femoral fracture cases have been observed in the clinical trial program 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 6: Hypercalcaemia in paediatric patients receiving denosumab and after treatment discontinuation

Hypercalcaemia in paediatric patients receiving denosumab and after treatment discontinuation has 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 potential risk 1: Fracture healing complications

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

Risk-benefit impact:

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

Important potential risk 2: Infection

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 infection, this use needs to be further studied.

Important potential risk 3: Cardiovasular event

This is a theoretical risk based on epidemiological data demonstrating elevated OPG 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 4: 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.

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

Based on the European Medicines Agency (EMA) guidance on similar biological medical products, the RMP should take into account identified risks and potential risks associated with the use of reference product, Prolia® (originator). Therefore, this section will contain all the important identified risks and important potential risks described in the RMP for the reference product, Prolia®.

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

Important Identified Risk: Hypocalcaemia

Potential mechanisms:

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

Evidence source(s) and strength of evidence:

Hypocalcaemia cases have been observed in the clinical trial program of the originator.

Characterisation of the risk:

Frequency: In the originator pooled pivotal studies for Postmenopausal osteoporosis (PMO) and Hormone ablation therapy (HALT) subject incidence of hypocalcaemia adverse events was < 0.1% in denosumab-treated subjects and 0.1% in placebo-treated subjects. The incidence of hypocalcaemia adverse events was lower in denosumab-treated subjects than in placebo-treated subjects; thus, 95% confidence intervals (Cls) were not calculated. In the 24-month final analysis of the glucocorticoid-induced osteoporosis (GIOP) study, subject incidence of hypocalcaemia adverse events was 0.3% in the denosumab group; there were no adverse events of hypocalcaemia in the risedronate group thus, 95% Cls were not calculated.

Severity: While most hypocalcaemia events are mild to moderate in severity; severe events have occurred.

Reversibility: Hypocalcaemia is reversible when treated with oral calcium and vitamin D supplementation. In severe cases, intravenous (IV) calcium supplementation may be required.

Long-term outcome: No long-term complications are anticipated for properly treated hypocalcaemia.

Impact on quality of life: For severe symptomatic hypocalcaemia, patients may be hospitalised for treatment. Generally, patients recover when their hypocalcaemia is treated.

Risk factors and risk groups:

Risk factors include severe renal impairment and hyperphosphatemia. Other risks factors may include a history of hypoparathyroidism, parathyroid hormone (PTH) resistance, vitamin D deficiency or resistance, thyroid surgery, parathyroid surgery, malabsorption syndromes, excision of small intestine, severe renal impairment (creatinine clearance (CrCL) < 30 mL/min)), dialysis, and some medications (Finkelstein, 2001).

Preventability:

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

Impact on the risk-benefit balance of the product:

The risk of hypocalcaemia has been considered in the product benefit-risk assessment. In light of the product labeling addressing this risk, the overall benefit-risk balance is considered to be positive.

Public health impact:

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

Important Identified Risk: Skin Infection Leading to Hospitalisation

Potential mechanisms:

Keratinocytes can express RANKL and blocking RANKL in mice decreased the number of regulatory T-cells in skin, leading to an increased inflammatory response (Loser, 2006 and Yamaguchi, 2006).

Evidence source(s) and strength of evidence:

Cases of skin infection leading to hospitalisation have been observed in the clinical trial program of the originator.

Characterisation of the risk:

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

adverse events of skin infection was 0.5% in both the denosumab and risedronate groups (HR [95% CI] = 1.03 [0.15, 7.34]).

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

Reversibility: These events typically resolved with administration of antibiotics.

Long-term outcome: No long-term complications are anticipated for properly treated patients who are hospitalised due to skin infections.

Impact on quality of life: Requires a hospital stay; patients generally recover with antibiotic treatment.

Risk factors and risk groups:

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

Preventability:

No preventive measures are known.

Impact on the risk-benefit balance of the product:

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

Public health impact:

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

Important Identified Risk: Osteonecrosis of the jaw

Potential mechanisms:

Osteonecrosis of the jaw appears to be multifactorial and multiple hypotheses have been postulated and have included factors such as inhibition of bone remodeling, 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 and Aghaloo, 2015).

Evidence source(s) and strength of evidence:

Osteonecrosis of the Jaw have been observed in the clinical trial program of the originator.

Characterisation of the risk:

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

Overall, across the originator-sponsored clinical development program for denosumab, positively adjudicated ONJ cases have been reported rarely (18 ONJ cases in 23,552 subjects, 0.076%) in subjects cumulatively exposed to denosumab (60 mg) clinical studies.

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

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

Long-term outcome: No data on long-term outcomes are available.

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

Risk factors and risk groups:

Risk factors include duration of exposure to denosumab, prior bisphosphonate use (particularly for extended periods of time), older age, periodontal disease, dentoalveolar surgery, trauma from poorly fitting dentures, malignancy, chemotherapy, corticosteroids, smoking, systemic or regional infection, immune-compromised state predisposing to increased risk of infection, hypercoagulable state secondary to underlying malignancy, and vascular insufficiency due to thrombosis (Mehrotra, 2006 and Ruggiero, 2006).

Preventability:

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

Impact on the risk-benefit balance of the product:

The risk of ONJ has been considered in the product benefit-risk assessment. In light of the product labeling and additional risk minimisation activities addressing this risk, the overall benefit-risk balance is considered to be positive.

Public health impact:

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

Important Identified Risk: Hypersensitivity Reactions

Potential mechanisms:

Two types of allergic reactions, IgE- and non-IgE-mediated, appear to be related to monoclonal antibody administration. The IgE-mediated reactions can cause both wheal and flare reactions at the injection site, but may also be associated with urticaria and anaphylaxis. The mechanism of non-IgE reactions is unclear.

Evidence source(s) and strength of evidence:

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

Characterisation of the risk:

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

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

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

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

Impact on quality of life: For severe hypersensitivity reactions, patients may be treated in the emergency room and/or hospitalised for treatment. Generally, patients recover when denosumab is discontinued with or without additional treatment.

Risk factors and risk groups:

Known hypersensitivity to denosumab and any of its excipients.

Preventability:

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

Impact on the risk-benefit balance of the product:

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

Public health impact:

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

Important Identified Risk: Atypical Femoral Fracture

Potential mechanisms:

Prolonged suppression of bone turnover may be associated with increased risk of AFF, but the pathogenesis remains unclear and the causes of AFF are likely multi-factorial. Based on

nonclinical studies, collagen cross-linking and maturation, accumulation of micro damage and advanced glycation end products, mineralisation, remodeling, vascularity, and angiogenesis lend biologic plausibility to a potential association between these effects and AFF (Ammar Ismail, 2018 and Shane, 2010).

Evidence source(s) and strength of evidence:

Atypical femoral fracture cases have been observed in the clinical trial program of the originator.

Characterisation of the risk:

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

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

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

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

Long-term outcome: No data on long-term outcomes are available.

Impact on quality of life: As with other femur fractures, AFF can cause short-term or long-term disability. Some data suggests that healing of AFF may be more prolonged than a typical femoral fracture (Bubbear, 2016 and Unnanuntana, 2013).

Risk factors and risk groups:

Long-term antiresorptive treatment has been associated with AFF. Corticosteroids have also been reported in the literature to potentially be associated with AFF (Meier, 2012 and Giusti, 2011). Atypical femoral fractures have also been reported in patients with certain comorbid conditions (e.g., vitamin D deficiency, RA, hypophosphatasia) and with use of bisphosphonates, glucocorticoids, and proton pump inhibitors (Shane, 2010).

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 has been considered in the product benefit-risk assessment. In light of the product labeling addressing this risk, the overall benefit-risk balance is considered to be positive.

Public health impact:

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

Important Identified Risk: Hypercalcemia in Paediatric Patients Receiving denosumab and After Treatment Discontinuation

Potential mechanisms:

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

- Hypercalcemia may result from rapid resorption of retained primary spongiosa in a skeleton with active endochondral ossification. The rate of endochondral ossification and duration of exposure to denosumab would determine the amount of accumulated primary spongiosa that could influence the magnitude of resorptive response (mechanostat-driven) and release of calcium from resorbing bone matrix via an autocrine/paracrine mechanism.
- The magnitude of the resorptive response following treatment and withdrawal in the immature skeleton could be dictated by the normal high rate of bone turnover in individuals with growing skeletons.
- The response of the osteoclast lineage to loss of inhibition of osteoclastogenesis may be intrinsically more robust in individuals with growing skeletons. The increased skeletal metabolism related to bone modeling and growth in children is therefore likely to impact the frequency of hypercalcemia occurring both between the dosing interval and following discontinuation.

Evidence source(s) and strength of evidence:

Hypercalcaemia in paediatric patients receiving denosumab and after treatment discontinuation has 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 originator completed paediatric osteogenesis imperfecta (OI) Study 20130173 (innovator study) during Q6M dosing regimen, hypercalcemia (Medical Dictionary for Regulatory Activities [MedDRA]; MedDRA Query [Narrow Search]) was reported for 29 subjects (19.0%). All these events were non-serious.

During every 3 months (Q3M) dosing regimen and following denosumab discontinuation, hypercalcemia was reported for 22 subjects (36.7%). Serious adverse events of hypercalcemia were reported for 8 subjects (13.3%).

Severity: Most subjects in the paediatric 01 Study 20130173 (innovator study) receiving the Q3M dosing regimen who had hypercalcemia events experienced mild events. Grade: 2: 3 hypercalcemia was reported for 10 subjects (16.7%). Grade 4 (life-threatening) hypercalcemia was reported for 4 subjects (6.7%).

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

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

Impact on quality of life: Paediatric patients may present with severe hypercalcemia requiring hospitalisation. Generally, patients recover when the hypercalcemia is treated.

Risk factors and risk groups:

Paediatric patients with growing skeletons and high bone turnover disease states.

Preventability:

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

Impact on the risk-benefit balance of the product:

The benefit-risk profile of denosumab is not favourable in the paediatric patient population.

Public health impact:

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

Important Potential Risk: Fracture Healing Complications

Potential mechanisms:

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

Evidence source(s) and strength of evidence:

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

Characterisation of the risk:

Frequency: Of the subjects who had non-vertebral fractures in the originator large pivotal PMO study, fracture healing complications (delayed healing or non-union) were reported in 2 of 386 subjects in the denosumab group (0.5%) and 5 of 465 subjects (1.1%) in the placebo group. Of the subjects who had non-vertebral fractures in the pivotal study for HALT-breast cancer, fracture healing complications were reported in 0 of 8 subjects in the denosumab group and 1 of 8 subjects (12.5%) in the placebo group. Because of the low incidence of fracture healing complications, 95% Cls were not calculated.

No fracture healing complications were reported in the male osteoporosis (MOP) study.

No fracture healing complications were reported in the GIOP study.

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

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

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

Impact on quality of life: Fracture healing complications can cause short-term or long-term disability. Surgery may be required.

Risk factors and risk groups:

General risk factors for fracture healing complications are thought to include older age, diabetes, use of medications such as non-steroidal anti-inflammatory drugs and corticosteroids, smoking, excessive alcohol use, and poor nutrition (Hernandez, 2012 and Gaston, 2007).

Preventability:

No preventive measures are known.

Impact on the risk-benefit balance of the product:

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

Public health impact:

No significant impact on public health is anticipated.

Important Potential Risk: Infection

Potential mechanisms:

Receptor activator of nuclear factor kappa-B ligand is expressed on activated T and B cells and in the lymph nodes and some reports have described immune modulatory effects of RANKL inhibition. However, no clinically relevant effect of denosumab treatment was observed on peripheral blood immune cell subset profiles in studies in healthy elderly men, postmenopausal women, and postmenopausal women with low bone mineral density. No evidence of a treatment effect of denosumab on Ig production was observed.

Evidence source(s) and strength of evidence:

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

Characterisation of the risk:

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

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

Reversibility: Infections when treated appropriately are generally reversible.

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

Impact on quality of life: For severe infection, patients may be hospitalised for treatment. Generally, patients recover when their infection is treated.

Risk factors and risk groups:

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

Preventability:

No preventive measures are known.

Impact on the risk-benefit balance of the product:

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

Public health impact:

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

Important Potential Risk: Cardiovascular Events

Potential mechanisms:

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

Evidence source(s) and strength of evidence:

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

Characterisation of the risk:

Frequency: In the originator pooled analysis of the large pivotal PMO study (20030216) and the pivotal HALT-prostate study, the overall subject incidence of adjudicated-positive serious cardiovascular events was 5.8% with denosumab and 5.6% with placebo (HR [95% CI] = 1.00 [0.85, 1.19]). The subject incidence of positively adjudicated, pre-defined categories of serious cardiovascular event was comparable between the treatment groups in the pooled analysis.

During the placebo-controlled phase of the pivotal study for MOP, adverse events in the cardiac disorders system organ class (SOC) were reported in 8 (6.7%) denosumab-treated and 3 (2.5%) placebo-treated subjects (note: 2 events of angina tonsillitis in the denosumab group were incorrectly coded to the cardiac disorders adverse event category). The incidence of adverse events in the vascular disorders SOC was 5.0% in denosumab-treated and 6.7% in placebo-treated subjects. In the GIOP study, adverse events in the cardiovascular disorders or vascular disorders SOC were reported in 65 (16.5%) denosumab-treated subjects and 53 (13.8%) risedronate-treated subjects (HR [95% CI] = 1.27 [0.88, 1.82]). Subject incidence of serious

adverse events in the cardiovascular or vascular SOC was 3.8% on the denosumab group and 3.9% in the risedronate group.

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

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

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

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

Impact on quality of life: Cardiovascular disease varies greatly in severity. For severe disease, patients may be hospitalised for treatment and disability may occur.

Risk factors and risk groups:

The denosumab development program comprises studies of older subject populations (e.g., osteoporosis, cancer) that are likely to have a higher incidence of pre-existing cardiovascular conditions and, thus, a higher incidence of cardiovascular toxicities than that of the general population (Schulz, 2004 and Hak, 2000).

Risk factors for atherosclerosis include age, sex, ethnicity, family history, elevated lipid levels, cigarette smoking, hypertension, diabetes, and concomitant medications, including antipsychotic agents and cyclooxygenase-2 inhibitors (Murphy, 2007 and Smith, 2004).

Preventability:

No preventive measures are known.

Impact on the risk-benefit balance of the product:

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

Public health impact:

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

Important Potential Risk: Malignancy

Potential mechanisms:

Receptor activator of nuclear factor kappa ligand is expressed on activated T and B cells and in the lymph nodes and some reports have described immune modulatory effects of RANKL inhibition; however, in vitro studies of RANK and RANKL activity on a wide range of human tumour types provide no evidence for carcinogenic risk associated with RANKL inhibition (Armstrong,

2008; Jones, 2006 and Mori, 2007). In in vivo rodent cancer models, RANKL inhibition has been shown to have a beneficial effect (Branstetter, 2008, Canon, 2008, Vanderkerken, 2003, Yonou, 2003 and Zhang, 2001).

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

Evidence source(s) and strength of evidence:

This is considered a potential risk based on 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 originator large pivotal PMO study, the subject incidence of new primary malignancy was 4.8% with denosumab and 4.3% with placebo (HR [95% CI] = 1.11 [0.90, 1.37]).

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

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

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

Severity: Malignancy is a clinically important event requiring medical intervention.

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

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

Impact on quality of life: Malignancy can be life-threatening and generally requires intervention e.g., surgery, radiation, and/or chemotherapy.

Risk factors and risk groups:

General factors for risk of malignancy include advancing age, diet, cigarette smoking, excessive ethanol consumption, and numerous environmental toxins. In addition, cancer populations are at increased risk for a second primary malignancy because of their existing malignancy, possible genetic predisposition, and exposure to chemotherapy and radiation treatment (Anand, 2008 and World Health Organization, 2010).

Preventability:

No preventive measures are known.

Impact on the risk-benefit balance of the product:

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

Public health impact:

Significant public health impact is not anticipated.

SVII.3.2. Presentation of the missing information

There is no missing information for denosumab.

Part II: Module SVIII - Summary of the safety concerns

The summary of safety concerns for Denosumab is based on the EU-RMP for Prolia® (originator) version 31.0; dated 11 January 2023 published on the 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	• Hypocalcaemia • Skin infection leading to hospitalisation • Osteonecrosis of the jaw • Hypersensitivity reactions • Atypical femoral fracture • Hypercalcemia in paediatric patients receiving denosumab and after treatment discontinuation
Important potential risks	• Fracture healing complications • Infection • Cardiovascular events • Malignancy
Missing information	None

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

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities 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 are presented below:

Specific adverse reaction follow-up questionnaires for safety concerns:

Hypocalcaemia

Purpose: To monitor the nature of hypocalcaemia in patients treated with denosumab in the post-marketing environment.

Skin infection leading to hospitalisation

Purpose: To monitor the nature of skin infections leading to hospitalisation and infections of any type reported in patients treated with denosumab in the post-marketing environment.

Osteonecrosis of the jaw

Purpose: To monitor the nature of ONJ in patients treated with denosumab in the post-marketing environment.

Atypical femoral fracture

Purpose: To monitor the nature of AFF reported in patients treated with denosumab in the post-marketing environment.

Fracture healing complications

Purpose: To monitor the nature of fracture healing complications reported in patients treated with denosumab in the post-marketing environment.

Malignancy:

Purpose: To monitor the nature of malignancy adverse events reported in patients treated with denosumab in the post-marketing environment.

Hypersensitivity reactions:

Purpose: To monitor the nature of hypersensitivity reported in patients treated with denosumab in the post-marketing environment.

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

Other forms of routine pharmacovigilance activities:

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

Not applicable.

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
Important Identified Risks	
Hypocalcaemia	Routine risk communication: • SmPC Sections 4.2, 4.3, 4.4, and 4.8 • Package leaflet (PL) Sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendation for correction of hypocalcaemia prior to initiating treatment with denosumab and clinical monitoring of calcium levels during treatment with denosumab is included in SmPC Section 4.4. Other routine risk minimisation measures beyond the Product Information: • Legal status: Denosumab is a medicinal product subject to restricted medical prescription.
Skin infection leading to hospitalisation	Routine risk communication: • SmPC Sections 4.4 and 4.8 • PL Sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk:

	• None Other routine risk minimisation measures beyond the Product Information: • Legal status: Denosumab is a medicinal product subject to restricted medical prescription.
Osteonecrosis of the jaw	Routine risk communication: • SmPC Sections 4.4 and 4.8 • PL Sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendation for oral examination, maintenance of good oral hygiene during treatment, management of patients with unavoidable invasive dental procedures, and temporary interruption of treatment if ONJ occurs is included in SmPC Section 4.4. Other routine risk minimisation measures beyond the Product Information: • Legal status: Denosumab is a medicinal product subject to restricted medical prescription.
Hypersensitivity reactions	Routine risk communication: • SmPC Sections 4.3 and 4.8 • PL Sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other routine risk minimisation measures beyond the Product Information: • Legal status: Denosumab is a medicinal product subject to restricted medical prescription.
Atypical femoral fracture	Routine risk communication: • SmPC Sections 4.4 and 4.8 • PL Sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk:

	• Recommendation for reporting new or unusual thigh, hip, or groin pain is included in SmPC Section 4.4. Other routine risk minimisation measures beyond the Product Information: • Legal status: Denosumab is a medicinal product subject to restricted medical prescription.
Hypercalcemia in paediatric patients receiving denosumab and after treatment discontinuation	Routine risk communication: • SmPC Sections 4.2, 4.4, and 4.8 • PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other routine risk minimisation measures beyond the Product Information: • Legal status: Denosumab is a medicinal product subject to restricted medical prescription.
Important Potential Risks	
Fracture healing complications	Routine risk communication: • SmPC Section 5.3 Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other routine risk minimisation measures beyond the Product Information: • Legal status: Denosumab is a medicinal product subject to restricted medical prescription.
Infection	Routine risk communication: • SmPC Section 4.8 • PL Section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other routine risk minimisation measures beyond the Product Information:

	• Legal status: Denosumab is a medicinal product subject to 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: Denosumab is a medicinal product subject to restricted medical prescription.
Malignancy	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: Denosumab is a medicinal product subject to restricted medical prescription.
Missing Information	
None	

Key: ONJ: Osteonecrosis of the jaw; PL: Package leaflet; SmPC: Summary of product characteristics

V.2. Additional Risk Minimisation Measures

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:

- the risk of ONJ during treatment with denosumab;

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

Target audience and planned distribution path:

Target audience will be the patients.

The patient reminder card will be distribution method will be agreed with each national authority before launching the product in respective countries.

Evaluation of the effectiveness of risk minimisation activities:

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.

Criteria for success:

No change in benefit risk profile.

V.3 Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risks		
Hypocalcaemia	Routine risk minimisation measures: • SmPC Section 4.4, where recommendation regarding correction and monitoring of calcium levels is provided • SmPC Sections 4.2, 4.3, and 4.8 • PL Sections 2 and 4 Legal status: Restricted medical prescription.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire for hypocalcaemia Additional pharmacovigilance activities: • None

	Additional risk minimisation measures: • None	
Skin infection leading to hospitalisation	Routine risk minimisation measures: • SmPC Sections 4.4, and 4.8 • PL Sections 2 and 4 Legal status: Restricted medical prescription. Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire for infection Additional pharmacovigilance activities: • None
Osteonecrosis of the jaw	Routine risk minimisation measures: • SmPC Section 4.4. where oral hygiene and dental management guidance is provided • SmPC Section 4.8 • PL 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: • Follow-up questionnaire for ONJ • External adjudication of events reported in clinical trials • Independent medical review of post-marketing study reports Additional pharmacovigilance activities: • None
Hypersensitivity reactions	Routine risk minimisation measures: • SmPC Sections 4.3 and 4.8 • PL Sections 2 and 4 Legal status: Restricted medical prescription. Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire for hypersensitivity Additional pharmacovigilance activities: None

Atypical femoral fracture	Routine risk minimisation measures: • SmPC Section 4.4, where recommendation for reporting potential symptoms is provided • SmPC Section 4.8 • PL Sections 2 and 4 Legal status: Restricted medical prescription. Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire for AFF • External adjudication of clinical trial cases • Independent medical review of post-marketing study reports Additional pharmacovigilance activities: • None
Hypercalcemia in paediatric patients receiving denosumab and after treatment discontinuation	Routine risk minimisation measures: • SmPC Sections 4.2, 4.4 and 4.8 • PL 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
Important Potential Risks		
Fracture healing complications	Routine risk minimisation measures: • SmPC Section 5.3 Legal status: Restricted medical prescription. Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire for fracture healing complications Additional pharmacovigilance activities: • None
Infection	Routine risk minimisation measures: • SmPC Section 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

	• PL Section 4 Legal status: Restricted medical prescription. Additional risk minimisation measures: • None	• Follow-up questionnaire for infection 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
Malignancy	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: • Follow-up questionnaire for malignancy Additional pharmacovigilance activities: • None
Missing information		
None		

Key: AFF: Atypical femoral fracture; ONJ: Osteonecrosis of the jaw; PL: Package leaflet; SmPC: Summary of product characteristics

Part VI: Summary of the risk management plan

Summary of risk management plan for Acvybra 60 mg solution for injection in pre-filled syringe (Denosumab)

This is a summary of the risk management plan (RMP) for Acvybra 60 mg solution for injection in pre-filled syringe (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 (PL) give essential information to healthcare professionals and patients on how Denosumab should be used.

This summary of the RMP for Denosumab should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

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

I. The medicine and what it is used for

Denosumab 60 mg solution for injection in pre-filled syringe is indicated for the treatment of:

- osteoporosis in postmenopausal women and in men at increased risk of fractures. In postmenopausal women denosumab significantly reduces the risk of vertebral, non-vertebral and hip fractures.
- bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. In men with prostate cancer receiving hormone ablation, denosumab significantly reduces the risk of vertebral fractures.
- bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture (see SmPC for the full indication).

It contains denosumab as the active substance and it is given by subcutaneous injection.

Further information about the evaluation of denosumab’s benefits can be found in Denosumab's EPAR, including in its plain-language summary, available on the European Medicines Agency (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 PL 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*.

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	• Hypocalcaemia • Skin infection leading to hospitalisation • Osteonecrosis of the jaw • Hypersensitivity reactions • Atypical femoral fracture • Hypercalcemia in paediatric patients receiving denosumab and after treatment discontinuation
Important potential risks	• Fracture healing complications • Infection • Cardiovascular events • Malignancy
Missing information	None

II.B Summary of important risks

Important identified risk: Hypocalcaemia	
Evidence for linking the risk to the medicine	Hypocalcaemia cases have been observed in the clinical trial program of the originator.
Risk factors and risk groups	Risk factors include severe renal impairment and hyperphosphatemia. Other risks factors may include a history of hypoparathyroidism, parathyroid hormone resistance, vitamin D deficiency or resistance, thyroid surgery, parathyroid surgery, malabsorption syndromes, excision of small intestine, severe renal impairment (creatinine clearance< 30 mL/min), dialysis, and some medications (Finkelstein, 2001).
Risk minimisation measures	Routine risk minimisation measures • SmPC Section 4.4, where recommendation regarding correction and monitoring of calcium levels is provided • SmPC Sections 4.2, 4.3, and 4.8 • PL Sections 2 and 4 Additional risk minimisation measures • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • None

Important identified risk: Skin infection leading to hospitalisation	
Evidence for linking the risk to the medicine	Cases of skin infection leading to hospitalisation have been observed in the clinical trial program of the originator.
Risk factors and risk groups	Risk factors for infection in general include increasing age, immunosuppression associated with cancer, diabetes, human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), immunosuppressant drugs (e.g., corticosteroids, arthritis medications, and chemotherapy drugs), substance abuse, and malnutrition. Risk factors for skin infection in older patients include skin wounds, peripheral vascular disease, eczema/dermatitis, and venous stasis disorders.
Risk minimisation measures	Routine risk minimisation measures • SmPC Sections 4.4, and 4.8 • PL Sections 2 and 4

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

Important identified risk: Osteonecrosis of the Jaw	
Evidence for linking the risk to the medicine	Osteonecrosis of the Jaw has been observed in the clinical trial program of the originator.
Risk factors and risk groups	Risk factors include duration of exposure to denosumab, prior bisphosphonate use (particularly for extended periods of time), older age, periodontal disease, dentoalveolar surgery, trauma from poorly fitting dentures, malignancy, chemotherapy, corticosteroids, smoking, systemic or regional infection, immune-compromised state predisposing to increased risk of infection, hypercoagulable state secondary to underlying malignancy, and vascular insufficiency due to thrombosis (Mehrotra, 2006 and Ruggiero, 2006).
Risk minimisation measures	Routine risk minimisation measures • SmPC Section 4.4, where oral hygiene and dental management guidance is provided • SmPC Section 4.8 • PL Sections 2 and 4 Additional risk minimisation measures • Patient reminder card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • None

Important identified risk: Hypersensitivity Reactions	
Evidence for linking the risk to the medicine	This risk was identified in the post-marketing setting of the originator based on a clinically plausible association between administration of denosumab and hypersensitivity reactions.
Risk factors and risk groups	Known hypersensitivity to denosumab and any of its excipients.
Risk minimisation measures	Routine risk minimisation measures • SmPC Sections 4.3 and 4.8

	• PL Sections 2 and 4 Additional risk minimisation measures • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • None

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.
Risk factors and risk groups	Long-term antiresorptive treatment has been associated with atypical femoral fracture. Corticosteroids have also been reported in the literature to potentially be associated with atypical femoral fracture (Meier, 2012 and Giusti, 2011) Atypical femoral fractures have also been reported in patients with certain comorbid conditions (e.g., vitamin D deficiency, rheumatoid arthritis, hypophosphatasia) and with use of bisphosphonates, glucocorticoids, and proton pump inhibitors (Shane, 2010).
Risk minimisation measures	Routine risk minimisation measures • SmPC Section 4.4, where recommendation for reporting potential symptoms is provided • SmPC Section 4.8 • PL Sections 2 and 4 Additional risk minimisation measures • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • None

Important identified risk: Hypercalcemia in paediatric patients receiving denosumab and after treatment discontinuation	
Evidence for linking the risk to the medicine	Hypercalcaemia in paediatric patients receiving denosumab and after treatment discontinuation has 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	Paediatric patients with growing skeletons and high bone turnover disease states (such as osteogenesis imperfecta).

Risk minimisation measures	Routine risk minimisation measures • SmPC Sections 4.2, 4.4, and 4.8 • PL Section 2 Additional risk minimisation measures • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • None

Important potential risk: Fracture healing complications	
Evidence for linking the risk to the medicine	This is a theoretical risk based on the potential mechanism of action.
Risk factors and risk groups	General risk factors for fracture healing complications are thought to include older age, diabetes, use of medications such as non-steroidal anti-inflammatory drugs and corticosteroids, smoking, excessive alcohol use, and poor nutrition (Hernandez, 2012 and Gaston, 2007).
Risk minimisation measures	Routine risk minimisation measures • SmPC Section 5.3 Additional risk minimisation measures • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • None

Important potential risk: Infection	
Evidence for linking the risk to the medicine	This is considered a potential risk based on theoretical concerns which has not been substantiated in the extensive clinical study program or in the post-marketing experience.
Risk factors and risk groups	Risk factors for infection in general include increasing age, immunosuppression associated with cancer, diabetes, HIV/AIDS, immunosuppressant drugs (e.g., corticosteroids, arthritis medications, and chemotherapy drugs), substance abuse, and malnutrition.
Risk minimisation measures	Routine risk minimisation measures • SmPC Section 4.8

	• PL Section 4 Additional risk minimisation measures • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • 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 (e.g., osteoporosis, cancer) that are likely to have a higher incidence of pre-existing cardiovascular conditions and, thus, a higher incidence of cardiovascular toxicities than that of the general population (Schulz, 2004 and Hak, 2000). Risk factors for atherosclerosis include age, sex, ethnicity, family history, elevated lipid levels, cigarette smoking, hypertension, diabetes, and concomitant medications, including antipsychotic agents and cyclooxygenase-2 inhibitors (Murphy, 2007 and Smith, 2004).
Risk minimisation measures	Routine risk minimisation measures • None Additional risk minimisation measures • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • 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.
Risk factors and risk groups	General factors for risk of malignancy include advancing age, diet, cigarette smoking, excessive ethanol consumption, and numerous environmental toxins. In addition, cancer populations are at increased risk for a second primary malignancy because of their existing malignancy, possible

	genetic predisposition, and exposure to chemotherapy and radiation treatment (Anand, 2008 and World Health Organization, 2010).
Risk minimisation measures	Routine risk minimisation measures • None Additional risk minimisation measures • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • None

II.C Post-authorisation development plan

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

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

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

There are no studies required for Denosumab.

Part VII: Annexes

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

Table of contents

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

- Hypocalcaemia
- Infection
- Osteonecrosis of the jaw
- Potential Atypical fracture
- Fracture healing
- Malignancy
- Hypersensitivity

Follow-up forms

Follow-up Form Title	Version Number	Date of Follow-up version
Hypocalcaemia	1.0	August 2024
Infection	1.0	August 2024
Osteonecrosis of the jaw	1.0	August 2024
Potential atypical fracture	1.0	August 2024
Fracture healing	1.0	August 2024
Malignancy	1.0	August 2024
Hypersensitivity	1.0	August 2024

DENOSUMAB - Specific Adverse Reaction Follow-up Questionnaire

Hypocalcaemia

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

Patient Identifier

Gender: ☐ Male ☐ Female
Weight:_____lb _____kg

Age at time of event: _____

Study No.

☐ Clinical Trial

☐ Post-marketing

Date of Event Onset

Date of This Report

Event Reported Term

Event Reported Term

Safety Database No.

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

Denosumab Indication

☐ Postmenopausal osteoporosis

☐ Bone loss from hormone ablation therapy

Please specify diagnosis_____

_____

☐ Advanced cancer with bone metastasis

Please specify cancer_____

☐ Other

Please specify_____

_____

☐ Don't know

Denosumab Dose

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

☐ Other Please specify_____

☐ Don't know

Denosumab Exposure

Denosumab first administered (date)

_____

Last denosumab dose before event (date)

_____

☐ Doses of denosumab were skipped

☐ 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

_____

SIGNS AND SYMPTOMS (Check all that apply)	DIAGNOSIS (Check all that apply)
☐ Numbness (Specify if involving digits and/peri-oral region) _____ ☐ Convulsions ☐ Muscle twitching ☐ Muscle cramping ☐ Paresthesia ☐ Syncope ☐ Tetany ☐ None ☐ Other _____	Serum calcium at time of event: _____ mg/dL ☐ Unknown Please provide serum albumin result _____ Serum albumin at the time of event < 4.0 g/dL? ☐ Yes ☐ No ☐ Unknown If yes, what were the ionised calcium levels? _____ mmol/dL Serum creatinine at time of event was > 2.0 X times upper limit of normal? (Please provide result): _____ ☐ Yes ☐ No ☐ Unknown Hypocalcemia-induced EKG changes (QT prolongation)? ☐ Yes ☐ No ☐ Unknown

Hypocalcaemia (Continued.)

TREATMENT

Treated only as an outpatient? ☐ Yes ☐ No

If yes, route of calcium replacement:

☐ IV ☐ Oral ☐ Unknown

Treated in the ER? ☐ Yes ☐ No

If yes, route of calcium replacement:

☐ IV ☐ Oral ☐ Unknown

Treatment included general hospital admission for calcium replacement?

☐ Yes ☐ No ☐ Unknown

If yes, route of calcium replacement:

☐ IV ☐ Oral ☐ Unknown

Treatment included ICU admission?

☐ Yes ☐ No ☐ Unknown

If yes, route of calcium replacement:

☐ IV ☐ Oral ☐ Unknown

Overall length of hospital stay:

☐ ≤1day ☐ >1day ☐ ≤7days ☐ >7days

Report to

Email:

Anti-arrhythmic medications? ☐ Yes ☐ No ☐ Unknown

If yes, please provide the details such as names and dates of treatment

Anti-arrhythmic medications _____

Other treatment? ☐ Yes ☐ No ☐ Unknown

If yes, specify: _____

REPORTER

Name:

Address:

City: State/

Country: Province:

Email: Postal code:

Phone (include country code)

Signature _____

Title _____ **Date** _____

Hypocalcaemia (Continued)

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

Patient Identifier	Patient Initials	Safety Database No.

RISK FACTORS (Check all that apply)

Medical History Risk Factors

Does the patient have any of the following risk factors: ☐ Yes ☐ No

If yes, please provide dates and details: _____

☐ Acute pancreatitis ☐ History of chronic renal disease _____

☐ History of parathyroid disease ☐ History of hypoalbuminemia _____

☐ History of malignancy (please specify) ☐ Hypoproteinemia _____

☐ Hyperphosphatemia ☐ Magnesium deficiency

☐ Recent surgery ☐ Sepsis

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

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

_____

☐ Prior hypocalcemia event (before denosumab treatment)

Please provide dates and details of prior hypocalcemia event

_____

Medication Risk Factors

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

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

Concomitant Medications

Taking vitamin D supplement? ☐ Yes ☐ No ☐ Unknown (Please provide dose and dates)

_____

_____

Taking calcium supplement? ☐ Yes ☐ No ☐ Unknown (Please provide dose and dates)

_____

_____

Other concomitant medications

_____

Hypocalcaemia Event Resolved ☐ Yes ☐ No ☐ Unknown

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

_____

REPORTER

Name:

Address:

City: State/

Country: Province:

Email: Postal code:

Phone (include country code)

Signature _____

Title _____ **Date** _____

Report to

Email:

DENOSUMAB - Specific Adverse Reaction Follow-up Questionnaire

Infection

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

Patient Identifier

Patient Initials

Date of Event Onset

Date of This Report

Gender: ☐ Male ☐ Female

Weight:_____lb _____kg

Age at time of event: _____

Event Reported Term

Study No.

☐ Clinical Trial

☐ Post-marketing

Safety Database No.

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

Denosumab Indication

☐ Postmenopausal osteoporosis

☐ Bone loss from hormone ablation therapy

Please specify diagnosis_____

_____

☐ Advanced cancer with bone metastasis

Please specify cancer_____

☐ Other Please specify_____

_____

☐ Don't know

Denosumab Dose

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

☐ Other (Please specify)_____

_____

☐ Don't know

Denosumab Exposure

Denosumab first administered (date)

_____

Last denosumab dose before event (date)

_____

☐ Doses of denosumab were skipped

☐ 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

_____

SIGNS AND SYMPTOMS (Check all that apply, provide dates of onset, resolution, if available)				
☐Fever _____ ☐Cough_____ ☐Swelling_____ Location_____ ☐Shortness of breath _____	☐Pain _____ Location_____ ☐Rash _____ Location _____ ☐Prolonged fatigue _____ ☐Diarrhea _____	☐Discharge_____ Location _____ Description _____ ☐Chills _____ ☐Night sweats ____ ☐Other _____	☐Organ system affected: ☐Cardiac ☐Ear/nose ☐Throat ☐Gastrointestinal ☐Respiratory	☐Musculoskeletal (including joints) ☐Nervous (cerebrospinal fluid) ☐Skin Location _____ ☐Kidney/genito-urinary ☐Systemic (bacteremia and/or sepsis) ☐Other _____

Infection (Continued.)

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

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

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

Infection (Continued.)

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

Patient Identifier	Patient Initials	Safety Database No.

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

CHECK WHICH INFECTION APPLIES

☐Cardiac infections

☐ Endocarditis
_____

☐ Pericarditis (purulent; tuberculous)
_____

☐ Other, please specify:
_____

☐Ear and labyrinth infections

☐ Otitis media
_____

☐ Oitis externa
_____

☐ Other, please specify:
_____

☐Gastrointestinal/abdominal infections

☐ Colitis
_____

☐ Diverticulitis
_____

☐ Appendicitis
_____

☐ Abdominal sepsis (including peritonitis)
____

☐ Hepatic abscess
_____

☐ Hepatitis B
_____

☐ Hepatitis C
_____

☐ Wound and skin infections

☐ Cellulitis
_____

☐ Erysipelas
_____

☐ Necrotising fasciitis
_____

☐ Abscess
_____

☐ Other skin infections, please specify:
_____

☐ Opportunistic infections

☐ Aspergillus (invasive forms only)
_____

☐ Blastomycosis pulmonary or extra-pulmonary infections _____

☐ Candidiasis systemic_____

☐ Coccidioidemycosis secondary/systemic_____

☐ Cryptococcal infection-pulmonary and non-pulmonary_____

☐ Cytomegalovirus-include systemic site
_____

☐ Herpes simplex (meningitis or encephalitis)
____

☐ Herpes zoster (only systemic or disseminated: involving 2 or more dermatomes)
_____

☐ Other, please specify:
_____

☐Musculoskeletal and connective tissue infections

☐ Osteomyelitis
_____

☐ Septic arthritis
_____

☐ Other, please specify:
_____

☐Nervous system infections

☐ Meningitis
_____

☐ Encephalitis
_____

☐ Other, please specify:
_____

☐Respiratory tract infections

☐ Pneumonia
_____

☐ Pulmonary TB
_____

☐ Lung abscess
_____

☐ Legionnella pneumonia
_____

☐ Mycoplasma pneumonia
_____

☐ Other, please specify:
_____

☐ Histoplasma infections - chronic disseminated or

severe acute
_____

☐ Mucormycosis (=zygomycosis) including infections due to Rhizopus, Mucor and Absidia of lung, genito-urinary tract, kidney, GIT, skin

_____

☐ Mycobacterium tuberculosis
_____

☐ Non-tuberculosis mycobacterium
_____

☐ Nocardia infection - of brain, lungs, kidney, skin

_____

☐ Paracoccidioides infections of lungs, skin other

_____

☐ Pneumocystis carinii pneumonia_____

☐ Sporotrichosis - disseminated infections
_____

☐ Toxoplasmosis encephalitis or disseminated
_____

☐ Other opportunistic infections, please specify:
____

Infection (Continued.)

☐Kidney and genito-urinary tract infections

☐ Cystitis
_____

☐ Pyelonephritis
_____

☐ Urinary tract infection
_____

☐ Other, please specify:
_____

☐Systemic infections

☐ Bacteremia
_____

☐ Sepsis
_____

☐ Toxic shock syndrome
_____

☐ Other, please specify: _____

☐ Other infections, please specify: _____

☐ Parasitic evaluation (ova, etc.)
_____

REPORTER

Name:

Address:

City: State/

Country: Province:

Email: Postal code:

Phone (include country code)

Signature _____

Title _____ **Date** _____

Report to

Email:

Infection (continued)

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

Patient Identifier	Patient Initials	Safety Database No.

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

DIAGNOSTICS

☐Cultures done ☐No ☐Yes ☐Unknown

If yes, check which apply:

☐Blood culture

_____

☐Culture positive ☐No ☐Yes ☐Unknown

If yes, which ☐Bacterial ☐Fungal ☐Viral

☐Pathogen identified:_____

☐Urine culture

☐Culture positive ☐No ☐Yes ☐Unknown

If yes, which ☐Bacterial ☐Fungal ☐Viral

☐Pathogen identified:_____

☐Sputum culture

☐Culture positive ☐No ☐Yes ☐Unknown

If yes, which ☐Bacterial ☐Fungal ☐Viral

☐Pathogen identified:_____

☐Cerebrospinal fluid culture

☐Culture positive ☐No ☐Yes ☐Unknown

If yes, which ☐Bacterial ☐Fungal ☐Viral

☐ Pathogen identified:

_____

☐Tissue culture

If yes, specify: ☐Brain ☐Lung ☐Liver

☐Kidney ☐Skin ☐Bone ☐Other

☐Culture positive ☐No ☐Yes ☐Unknown

If yes, which ☐Bacterial ☐Fungal ☐Viral

☐Pathogen identified:

_____

☐Catheter Tip/Line _____

☐Culture positive ☐No ☐Yes ☐Unknown

If yes, which ☐Bacterial ☐Fungal ☐Viral

☐Pathogen identified:

_____

☐PPD placement ☐No ☐Yes ☐Unknown

If yes, PPD positive ☐No ☐Yes ☐Unknown

_____

☐Parasttic evaluation (ova, etc.)__

☐X-ray ☐No ☐Yes ☐Unknown

☐MRI ☐No ☐Yes ☐Unknown

☐CT scan ☐No ☐Yes ☐Unknown

_____

☐Bone scan No ☐Yes ☐Unknown

_____

☐ Other_____

☐ Rapid test_____

☐ Serum titres_____

☐ Hospital discharge report

_____

☐ Other consult report

_____

_____

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

_____

☐Outcome and resolution date_____

☐Synovial culture _____

☐Culture positive ☐No ☐Yes ☐Unknown

If yes, which ☐Bacterial ☐Fungal ☐Viral

☐Pathogen identified:_____

TREATMENT

☐ER antibiotics ☐No ☐Yes ☐Unknown

If yes, route

☐IV ☐Oral ☐SC ☐Both oral and IV

☐Required hospital admission

☐No ☐Yes ☐Unknown

☐ ICU admission

☐ No ☐Yes ☐Unknown

If yes, reason for ICU admission_____

Overall length of hospital stay

☐<1 day ☐>1day or ☐<7 days ☐>7 days

_____

☐In-hospital antibiotics

☐No ☐Yes ☐Unknown

☐If yes, route of administration

☐IV ☐Oral ☐Both oral and IV

☐Other in-hospital treatment

☐Antivirals ☐No ☐Yes ☐Unknown

If yes, route of administration

☐IV ☐Oral

☐Antifungals ☐No ☐Yes ☐Unknown

If yes, route of administration

☐IV ☐Oral

☐Surgery ☐No☐Yes ☐Unknown

☐Hyperbaric oxygen ☐No ☐Yes ☐Unknown

Infection (continued.)

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

Please specify any post-operative complications, chronic disease or infection, etc.

☐Chronic lung disease_____

☐Hepatitis_____

☐Chronic kidney disease_____

☐Liver disease_____

☐Congenital infections/malformations____

☐Osteomyelitis_____

☐HIV_____

☐Diabetes mellitus_____

☐Cancer (specify)_____

☐Recent wounds/infections_____

☐Immunosuppression_____

☐Known exposure to TNF inhibitors__

☐Chemotherapy

Exposure to infectious agents (continued)

☐Hospital acquired_____

☐Other_____

☐Steroid exposure_____

☐Insect/tick bite_____

☐Drug or IV drug abuse:
Type_____

Amount_____

Frequency_____

☐Alcohol/Tobacco use:
Type_____
Amount_____
Frequency_____

☐Indwelling catheters_____

☐Recent skin injury _____

☐Recent travel (specify)_____

Exposure to animals/zoonotic diseases (exposure to infected animal)_____

☐Unprotected sex _____

☐Immobility _____

☐Indwelling catheters _____

☐Nursing home resident_____

☐Occupational exposure _____

☐Ostomy _____

☐Post influenza _____

☐Surgery < 30 days _____

☐TB Exposure

☐Other history/risk factors

☐Malnutrition/failure to thrive_____

☐Exposure to infectious agents_____

☐ Personal contact___ Body fluids___

☐Share personal items (razor, needles etc.,)_____

☐Potentially contaminated food/liquid____

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

Osteonecrosis of the Jaw

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

Patient Identifier

Patient Initials

Date of Event Onset

Date of This Report

Gender: ☐ Male ☐ Female

Weight:_____lb _____kg

Age at time of event: _____

Event Reported Term

Study No.

Safety Database No.

☐ Clinical Trial

☐ Post-marketing

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

Denosumab Indication

☐ Postmenopausal osteoporosis

☐ Bone loss from hormone ablation therapy

Please specify diagnosis_____

_____

☐ Advanced cancer with bone metastasis

Please specify cancer_____

☐ Other Please specify_____

_____

☐ Don't know

Denosumab Dose

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

☐ Other (Please specify)_____ _____

☐ Don't know

Denosumab Exposure

Denosumab first administered (date)

_____

Last denosumab dose before event (date)

_____

☐ Doses of denosumab were skipped

☐ Yes ☐ No ☐ Unknown

If yes, please specify

_____

☐ Doses of denosumab given after event began

☐ Yes ☐ No ☐ Unknown

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

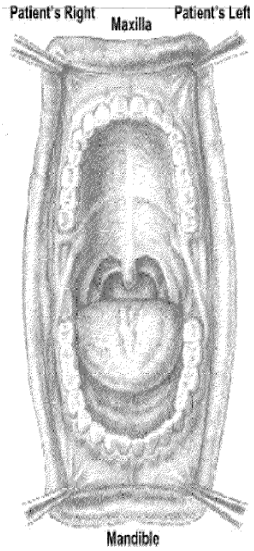
_____

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**
_____

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_____
Hospitalisations ☐ No ☐ Yes ☐ Unknown If yes, reason for hospitalisation _____
Hospitalisation begin date _____ Hospitalisation 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)/dose_____
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:

Patient Reminder Card Status (for EU Patients)

Received a patient reminder card prior to the ONJ event:

☐ Yes ☐ No ☐ Unknown

_____

_____

DENOSUMAB - Specific Adverse Reaction Follow-up Questionnaire

Potential Atypical Fracture

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

Patient Identifier	Patient Initials	Date of Event Onset	Date of This Report

Gender: ☐ Male ☐ Female
Weight:_____lb _____kg
Age at 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

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

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)
☐ Unknown type of trauma

Potential Atypical Fracture (Continued.)

DIAGNOSIS (Check all that apply)

☐ 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 breaking of the
Cortex:

☐ Yes ☐ No ☐ Not reported

Diffuse cortical thickening of proximal femoral shaft:

☐ Yes ☐ No ☐ Not reported

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

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

Potential Atypical Fracture (Continued.)

Past medical and surgical history: _____
_____
Medical history (include dose, frequency, and dates of treatment): _____
_____
Copies of records/consults/radiology report attached
☐Yes ☐ No
_____
_____

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

Fracture Healing

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

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

Gender: ☐ Male ☐ Female Weight: __ lb __kg

Age at time of event: _____

Event Reported Term

Study No.

☐ Clinical Trial
☐ Post-marketing

Safety Database No.

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

Denosumab Indication

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

Denosumab Dose

☐ 60 mg SC every 6 months ☐ 120 mg SC every 4 weeks
☐ Other (Please specify)_____ ☐ Don't know

Denosumab Exposure

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

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

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

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

☐ Cervical spine
☐ Clavicle
☐ Hand/Metacarpal/Phalange
☐ Head/Face/Skull
☐ Humerus
☐ Olecranon
☐ Radius
☐ Rib
☐ Scapula
☐ Shoulder
☐ Sternum
☐ Ulna
☐ Wrist/Carpal

☐Other _____

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

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

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

☐ Severe trauma (e.g., falling from roof, motor vehicle accident)

☐ Minimal trauma (e.g., falling from standing position or less)

☐ Non-traumatic

Characteristics of fracture (check all that apply):

☐ Comminuted

☐ Compound

☐ Pathologic

☐ Poor alignment

☐ Poor immobilisation of segments

☐ Soft tissue injury

☐ Unknown

DENOSUMAB - Specific Adverse Reaction Follow-up Questionnaire

Fracture Healing (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 (check all that apply):

☐ Casting _____

☐ Non-surgical reduction_____

☐ Revision surgery (2nd surgery) _____

☐ Surgery _____

☐ Traction_____

☐ Other_____

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

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

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

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

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

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

☐Current smoker/tobacco use

_____

_____

☐History or current corticosteroid use

_____

_____

☐Prior fracture history

_____

_____

_____

☐Diabetes

_____

_____

_____

_____

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

Malignancy

Patient Identifier_____ Patient Initials_____ AER No. _____

Questionnaire for Malignancy Adverse Events

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

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

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

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

If yes, date of prior cancer (dd/mm/yyyy): ___/___/___

Tumor stage, if known: _____

Primary site of malignancy: _____

Tumor Stage:

Tumor Size (Check which one applies):

TX ☐ T0 ☐ Tis ☐ T1 ☐ T2 ☐ T3 ☐ T4 ☐

Tumor Grade (Check which one applies):

GX ☐ G1 ☐ G2 ☐ G3 ☐

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

(If yes, skip next 2 questions)

Lymph Node Involvement (Check which one applies):

NX ☐ N1 ☐ N2 ☐ N3 ☐

Metastases (Check which one applies):

MX ☐ M0 ☐ M1 ☐

Malignancy (Continued.)

TREATMENT:

Hospitalised? Yes ☐ No ☐ Unknown ☐

ICU admission? Yes ☐ No ☐ Unknown ☐

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

Surgical treatment? Yes ☐ No ☐ Unknown ☐

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

Hormonal treatment? Yes ☐ No ☐ Unknown ☐

Radiation treatment? Yes ☐ No ☐ Unknown ☐

Bone marrow transplant? Yes ☐ No ☐ Unknown ☐

If yes, autologous ☐ heterologous ☐

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

RISK FACTORS (Check all that apply):

Smoking ☐

Prior Malignancy ☐

Positive Family History (Check all that apply):

Same cancer ☐

Different cancer ☐

Prior therapeutic radiation exposure ☐

Environmental exposure ☐

Specify: _____

DENOSUMAB - Specific Adverse Reaction Follow-up Questionnaire

Hypersensitivity

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

Patient Identifier	Patient Initials	Date of Event Onset	Date of This Report

Gender: ☐ Male ☐ Female
Weight:_____lb_____kg

Age at time of event: _____

Event Reported Term

Study No.

☐ Clinical Trial
☐ Post-marketing

Safety Database No.

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

Denosumab Indication

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

Denosumab Dose

☐ 60 mg SC every 6 months ☐ 120 mg SC every 4 weeks
☐ Other (Please specify)_____ ☐ Don't know

Denosumab Exposure

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

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

SIGNS AND SYMPTOMS (Check all that apply)

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

Hypersensitivity (Continued.)

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

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

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

DENOSUMAB - Specific Adverse Reaction Follow-up Questionnaire

Hypersensitivity (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)

☐ ER Corticosteroids
Route: ☐ IV ☐ Oral

☐ ER anti-histaminics
Route: ☐ IV only ☐ oral only ☐ both oral and IV

☐ Required hospital admission ☐ Yes ☐ No
Overall length of hospital stay
☐< 1 day ☐ > 1 day or < 7 days ☐ > 7 days

☐ICU admission ☐ Yes ☐ No ☐ Unknown
Overall length of hospital stay
☐< 1 day ☐ > 1 day or < 7 days ☐ > 7 days

☐In-hospital corticosteroids
Route: ☐ IV only ☐ oral only ☐ both oral and IV

☐In hospital anti-histaminics
Route: ☐ IV only ☐ oral only ☐ both oral and IV

☐Other in-hospital treatment
☐ IV vasopressors ☐ Yes ☐ No ☐ Unknown
☐ Intubation/mechanical ventilation ☐Yes ☐No ☐ Unknown

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

CONCOMITANT MEDICATIONS

☐ ACE inhibitors	☐ IV contrast
☐ Allopurinol	☐ NSAIDS/Aspirin
☐ Cancer chemotherapy	☐ Penicillamine
☐ Dapsone	☐ Rifampin

☐Anticonvulsants (check which apply):
☐Phenytoin
☐Carbamazepine
☐Phenobarbital

☐Antibiotics (check which apply)
☐Beta-lactams including penicillin and cephalosporin
☐Macrolides
☐Sulfonamides
☐Quinolones

☐ Hypersensitivity event resolved ☐ Yes ☐ No ☐ Unknown
If yes, date (DD/MM/YYYY):
_____

☐Final diagnosis or etiology (Incl. start date) please send supporting documents for diagnosis
_____

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

Report to Email:	**REPORTER** Name: Address: City: State/ Country: Province: Email: Postal code: Phone (include country code) **Signature** _____ **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 (if applicable)

Approved key messages of the additional risk minimisation measures

Patient reminder card:

Patient Reminder Cards for osteonecrosis of the jaw (ONJ) will be distributed to the patients.

The patient reminder card distribution method will be agreed with each national authority before launching the product.

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:

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

Annex 7 - Other supporting data (including referenced material)

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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 Centralised: H0006492	New application
0.2	Not applicable EMEA/H/C/006734/0000	Following changes made: Invented name in the EEA and procedure number updated – "Acvybra 60 mg solution for injection in pre-filled syringe" – Centralised (EMEA/H/C/006734/0000)