# EU Risk Management Plan

# For

# Kefdensis 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: 31-JAN-2024

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Qualified Person Responsible for Pharmacovigilance (QPPV) name: Dr. Andreas Iwanowitsch

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV. The electronic signature is available on file.

# Table of content

# Part I: Product(s) Overview

Table Part I.1 – Product(s) Overview

| | |
|---|---|
| **Active substance(s) (International non-proprietary name or common name)** | Denosumab. |
| **Pharmacotherapeutic group(s) (Anatomical Therapeutic Chemical classification [ATC] Code)** | Drugs for treatment of bone diseases – Other drugs affecting bone structure and mineralisation,<br>ATC code: M05BX04 |
| **Marketing Authorisation Holder (MAH)** | STADA Arzneimittel AG |
| **Medicinal products to which this Risk Management Plan (RMP) refers** | 1. |
| **Invented name(s) in the European Economic Area (EEA)** | Kefdensis 60 mg solution for injection in pre-filled syringe |
| **Marketing authorisation procedure** | Centralised procedure. |
| **Brief description of the product** | Chemical class:<br>Denosumab is a human monoclonal antibody of the immunoglobulin G (IgG) 2 subclass. |
| | Summary of mode of action:<br>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), preventing activation of its receptor, RANK, on the surface of osteoclast precursors and osteoclasts. 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:<br>Denosumab is a human monoclonal IgG2 antibody produced in a mammalian cell line (Chinese hamster ovary cells) by recombinant deoxyribonucleic acid (DNA) technology. |
| **Hyperlink to the Product Information** | Please refer to Module 1.3.1. |

| | |
|---|---|
| **Indication(s) in the EEA** | Current:<br>Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures. In postmenopausal women Kefdensis significantly reduces the risk of vertebral, non-vertebral and hip fractures.<br>Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. In men with prostate cancer receiving hormone ablation, {(Invented) name} significantly reduces the risk of vertebral fractures.<br>Treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture. |
| | Proposed (if applicable): not applicable. |
| **Dosage in the EEA** | Current:<br>Kefdensis 60 mg solution for injection in pre-filled syringe:<br>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):<br>Kefdensis 60 mg solution for injection in pre-filled syringe<br>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)

Not applicable. Omitted module for biosimilar products.

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

Kefdensis (denosumab) has been developed as a proposed biosimilar to US-licensed Prolia® and to EU-approved Prolia® (the originator). The non-clinical development program for Kefdensis has been designed in accordance with the current regulatory requirements for the non-clinical development of biosimilar monoclonal antibodies:

- EMA/CHMP/BMWP/403543/2010: Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues
- FDA Guidance for Industry: Scientific Considerations in demonstrating Biosimilarity to a reference product, April 2015

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

Key safety findings from non-clinical studies and relevance to human usage:

**Toxicity**

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

**Safety Pharmacology**

No studies to evaluate safety pharmacology of Kefdensis 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 clinical trials have been conducted with denosumab since the Development International Birth Date (DIBD).

Ongoing studies:

AVT03-GL-P01

A randomized, 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.

AVT03-GL-C01

A randomized, 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

**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 osteonecrosis of the jaw associated with the use of denosumab is currently in section 4.4 "Special warnings and precautions for use" of the SmPC) and section 4.8 "Undesirable effects" of the SmPC

**Hypersensitivity to the active substance or any of the excipients**

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

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

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

**Atypical femoral fracture**

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

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

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

**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 localized 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 | |
| Patients with relevant comorbidities:<br>• Patients with hepatic impairment<br>• Patients with renal impairment<br>• Patients with cardiovascular impairment<br>• Immunocompromised patients<br>• 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 product is not commercialised.

# 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.
- Infections and infestations: Urinary tract infection, Upper respiratory tract infection, Diverticulitis, Cellulitis, Ear infection.
- 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.

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

- Immune system disorders: Drug hypersensitivity.
- Metabolism and nutrition disorders: Hypocalcaemia.
- Musculoskeletal and connective tissue disorders: Osteonecrosis of the jaw, Atypical femoral fractures.

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 osteoprotegerin in patients with cardiovascular disease.

Risk-benefit impact:

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

**Important potential risk 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

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

**Important identified risk 1: 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:

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 (CIs) were not calculated. In the 24-month final analysis of the glucocorticoid-induced osteoporosis (GlOP) 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% CIs were not calculated. While most hypocalcaemia events are mild to moderate in severity; severe events have occurred. Hypocalcaemia is reversible when treated with oral calcium and vitamin D supplementation.

In severe cases, intra-venous (IV) calcium supplementation may be required. No long-term complications are anticipated for properly treated hypocalcaemia. For severe symptomatic hypocalcaemia, patients may be hospitalized for treatment. Generally, patients recover when their hypocalcaemia is treated.

Risk factors and risk groups:

Risk factors include severe renal impairment (creatinine clearance (CrCL) < 30 mL/min) 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, 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 2: Skin Infection Leading to Hospitalisation**

Potential mechanisms:

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

Evidence source(s) and strength of evidence:

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

Characterisation of the risk:

In the originator pooled PMO/HAL T 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% Cl: 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% Cl] = 2.55 [1.13, 5.76]). In the 24-month final analysis of the GlOP 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% Cl = 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% Cl] = 1.03 [0.15, 7.34]). Serious adverse events of skin infection were mostly severe in intensity. These events typically resolved with administration of antibiotics. No long-term complications are anticipated for properly treated patients who are hospitalized due to skin infections. 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, 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 3: Osteonecrosis of the Jaw**

Potential mechanisms:

Osteonecrosis of the jaw (ONJ) appears to be multifactorial and multiple hypotheses have been postulated and have included factors such as inhibition of bone 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 et al, 2017; Aghaloo et al, 2015).

Evidence source(s) and strength of evidence:

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

Characterisation of the risk:

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 GlOP study. Overall, across the Amgen-sponsored clinical development program for originator, positively adjudicated ONJ cases have been reported rarely (18 ONJ cases in 23552 subjects, 0.076%) in subjects cumulatively exposed to denosumab (60 mg) clinical studies. Most events leading to adjudication as ONJ were assessed as moderate in severity. Mild and severe events were also reported. In general, ONJ events are clinically reversible with supportive care, antibiotics; however, surgical treatment may be required. No data on long-term outcomes are available. Discomfort associated with ONJ lesions and/or with more extensive treatments may impact patient wellbeing via decreased oral intake (e.g., decreased hydration and decreased nutritional intake).

Risk factors and risk groups:

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

to underlying malignancy, and vascular insufficiency due to thrombosis (Mehrotra and Ruggiero, 2006; Ruggiero et al, 2006).

Preventability:

A dental examination with appropriate preventive dentistry is recommended prior to treatment with originator, 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 originator should receive care by a dentist or an oral surgeon. In patients who develop ONJ during treatment with originator, 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 osteonecrosis of the jaw has been considered in the product benefit-risk assessment. In light of the product labeling and additional risk minimization 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 originator, as the event is rare and the actions taken to minimize the likelihood of developing ONJ are described in the prescribing information.

**Important identified risk 4: Hypersensitivity Reactions**

Potential mechanisms:

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

Evidence source(s) and strength of evidence:

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

Characterisation of the risk:

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]). Most hypersensitivity reactions are mild to moderate in severity; severe events have occurred. Hypersensitivity reactions are generally reversible with discontinuation of the medication, though treatment may be required. No long-term complications are anticipated for properly treated hypersensitivity reactions. For severe hypersensitivity reactions, patients may be treated in the emergency room and/or hospitalized for treatment. Generally, patients recover when denosumab is discontinued with or without additional treatment.

Risk factors and risk groups:

Known hypersensitivity to denosumab and any of its excipients

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 5: Atypical Femoral Fracture**

Potential mechanisms:

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

Evidence source(s) and strength of evidence:

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

Characterisation of the risk:

No cases of confirmed AFF have been reported in the originator placebo-controlled studies; thus, 95% CIs were not calculated. In the GlOP 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% CIs 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 of the originator. 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 originator studies leading to adjudication of AFF were considered as severe in intensity. 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. No data on long-term outcomes are available. As with other femur fractures, AFF can cause short-term or long-term disability. Some data suggests that healing of AFF may be more prolonged than a typical femoral fracture (Bubbear, 2016; Unnanuntana et al, 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 et al, 2012; Giusti et al, 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 et al, 2010).

Preventability:

No data are currently available on potential measures to prevent AFF. Patients using long-term anti-resorptives 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 atypical femoral fracture 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:

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

**Important identified risk 5: Hypercalcaemia in Paediatric Patients Receiving Denosumab and After Treatment Discontinuation**

Potential mechanisms:

The exact mechanism of hypercalcaemia 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:

- Hypercalcaemia 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 hypercalcaemia 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:

In the originator completed paediatric osteogenesis imperfect (OI) Study 20130173 during the Q6M (every 6 months) dosing regimen, hypercalcaemia (Amgen Medical Dictionary for Regulatory Activities [MedDRA] Query [Narrow Search; AMQN]) was reported for 29 subjects (19.0%). All these events were nonserious. During the Q3M (every 3 months) dosing regimen and following denosumab discontinuation, hypercalcaemia (AMQN) was reported for 22 subjects (36.7%). Serious adverse events of hypercalcaemia were reported for 8 subjects (13.3%). Most subjects in the paediatric OI Study 20130173 receiving the Q3M dosing regimen who had hypercalcaemia events experienced mild events. Grade ≥3 hypercalcaemia was reported for 10 subjects (16.7%). Grade 4 (life-threatening) hypercalcaemia was reported for 4 subjects (6.7%). Hypercalcaemia is reversible when treated. In severe cases, use of

rescue medications may be required. No long-term adverse effects are anticipated for properly treated hypercalcaemia. Paediatric patients may present with severe hypercalcaemia requiring hospitalization. Generally, patients recover when the hypercalcaemia 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 of the originator, such as for paediatric GlOP, 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 favorable 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 1: 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:

Of the subjects who had nonvertebral fractures in the originator large pivotal PMO study, fracture healing complications (delayed healing or nonunion) 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 nonvertebral 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% CIs were not calculated. No fracture healing complications were reported in the MOP study. No fracture healing complications were reported in the GlOP study. This risk has not been substantiated; however, impaired fracture healing could have significant impact on patient wellbeing. This risk has not been substantiated; however, the effects of denosumab on osteoclasts are fully reversible. This risk has not been substantiated; however, no long-term impact would be anticipated based on reversibility. Fracture healing complications can cause short-term or long-term disability. Surgery may be required.

Risk factors and risk groups:

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

Preventability:

No preventive measures are known.

Impact on the risk-benefit balance of the product:

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

Public health impact:

No significant impact on public health is anticipated.

**Important potential risk 2: Infection**

Potential mechanisms:

RANK ligand is expressed on activated T and B cells and in the lymph nodes and some reports have described immune modulatory effects of RANKL inhibition. However, no clinically relevant effect of denosumab treatment was observed on peripheral blood immune cell subset profiles in studies in healthy elderly men, postmenopausal women, and postmenopausal women with low BMD. No evidence of a treatment effect of denosumab on immunoglobulin production was observed.

Evidence source(s) and strength of evidence:

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

Characterisation of the risk:

In the originator 24-month final analysis of the GlOP 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]). The majority of reported events of infection were non serious. Serious adverse events were most commonly reported as severe in intensity. Infections when treated appropriately are generally reversible. Infection generally responds to appropriate treatment and as such no long-term effects are anticipated. For severe infection, patients may be hospitalized for treatment. Generally, patients recover when their infection is treated.

Risk factors and risk groups:

Risk factors for infection in general include increasing age, immunosuppression associated with cancer, diabetes, HIV/AIDS, immunosuppressant drugs (eg, 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 3: 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 osteoprotegerin in patients with cardiovascular disease.

Characterisation of the risk:

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]). 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 20190038 (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 MI-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). This risk has not been substantiated; however, cardiovascular events may be severe/life-threatening. This risk has not been substantiated; however, effects of denosumab to block RANKL are fully reversible. This risk has not been substantiated; however, cardiovascular events could impact patient long-term outcome. Cardiovascular disease varies greatly in severity. For severe disease, patients may be hospitalized for treatment and disability may occur.

Risk factors and risk groups:

The denosumab development program of the originator comprises studies of older subject populations (e.g., osteoporosis, cancer) that are likely to have a higher incidence of pre-existing cardiovascular conditions and, thus, a higher incidence of cardiovascular toxicities than that of the general population (Schulz et al, 2004; Hak et al, 2000). Risk factors for atherosclerosis include age, sex, ethnicity, family history, elevated lipid levels, cigarette smoking, hypertension, diabetes, and concomitant medications, including antipsychotic agents and COX-2 inhibitors (Murphy and Dargie, 2007; Smith et al, 2004 ).

Preventability:

No preventive measures are known.

Impact on the risk-benefit balance of the product:

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

Public health impact:

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

**Important potential risk 4: Malignancy**

Potential mechanisms:

RANK ligand is expressed on activated T and B cells and in the lymph nodes and some reports have described immune modulatory effects of RANKL inhibition; however, in vitro studies of RANK and RANKL activity on a wide range of human tumor types provide no evidence for carcinogenic risk associated with RANKL inhibition (Armstrong et al, 2008; Jones et al, 2006; Mori et al, 2007). In in vivo rodent cancer models, RANKL inhibition has been shown to have a beneficial effect (Branstetter et al, 2008; Canon et al, 2008a, 2008b; Vanderkerken et al, 2003; Yonou et al, 2003; Zhang et al, 2001 ).

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

Evidence source(s) and strength of evidence:

This is considered a potential risk based on 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:

In the originator large pivotal PMO study (20030216), 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 pivotal HALT prostate cancer study (20040138), 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 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 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. Malignancy is a clinically important event requiring medical intervention. Although some malignancies will respond to treatment, long-term survival will depend upon multiple factors and as such onset of malignancy is rarely considered reversible. New primary malignancy or progression of existing malignancy may be fatal, life-threatening and long-term outcomes will likely be impacted. Malignancy can be life-threatening and generally requires intervention (e.g. surgery, radiation, and/or chemotherapy).

Risk factors and risk groups:

General factors for risk of malignancy include advancing age, diet, cigarette smoking, excessive ethanol consumption, and numerous environmental toxins. In addition, cancer populations are at increased risk

for a second primary malignancy because of their existing malignancy, possible genetic predisposition, and exposure to chemotherapy and radiation treatment (Anand et al, 2008; World Health Organization [WHO], 2010).

Preventability:

No preventive measures are known.

Impact on the risk-benefit balance of the product:

The potential risk of malignancy has been considered in 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

Table SVIII.1: Summary of safety concerns

| **Summary of safety concerns** | |
|---|---|
| **Important identified risks** | Hypocalcaemia<br>Skin infection leading to hospitalisation<br>Osteonecrosis of the jaw<br>Hypersensitivity reactions<br>Atypical femoral fracture<br>Hypercalcaemia in paediatric patients receiving denosumab and after treatment discontinuation |
| **Important potential risks** | Fracture healing complications<br>Infection<br>Cardiovascular events<br>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:

**Specific Adverse Reaction Follow-up Questionnaires**

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

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

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

**Other Forms of Routine Pharmacovigilance Activities for safety concerns**

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

## 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 |
|---|---|
| Hypocalcaemia | Routine risk communication:<br>SmPC sections 4.2, 4.3, 4.4 and 4.8.<br>Patient Information Leaflet (PIL) sections 2 and 4.<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>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.<br>In order to inform patients of this risk, corresponding text is also present in the PIL sections 2 and 4.<br>Other routine risk minimisation measures beyond the Product Information:<br>Legal status: Restricted medical prescription. |
| Skin infection leading to hospitalisation | Routine risk communication:<br>SmPC sections 4.4 and 4.8.<br>PIL sections 2 and 4.<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>None<br>Other routine risk minimisation measures beyond the Product Information:<br>Legal status: Restricted medical prescription. |
| Osteonecrosis of the jaw | Routine risk communication:<br>SmPC sections 4.4 and 4.8<br>PIL sections 2 and 4.<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>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.<br><br>In order to inform patients of this risk, corresponding text is also present in the PIL sections 2 and 4.<br><br>Other routine risk minimisation measures beyond the Product Information:<br><br>Legal status: Restricted medical prescription. |
| Hypersensitivity reactions | Routine risk communication:<br><br>SmPC sections 4.3 and 4.8.<br><br>PIL sections 2 and 4.<br><br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br><br>None<br><br>Other routine risk minimisation measures beyond the Product Information:<br><br>Legal status: Restricted medical prescription. |
| Atypical femoral fracture | Routine risk communication:<br><br>SmPC sections 4.4 and 4.8.<br><br>PIL sections 2 and 4.<br><br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br><br>Recommendation for reporting new or unusual thigh, hip, or groin pain is included in SmPC Section 4.4.<br><br>In order to inform patients of this risk, corresponding text is also present in the PIL sections 2 and 4.<br><br>Other routine risk minimisation measures beyond the Product Information:<br><br>Legal status: Restricted medical prescription. |
| Hypercalcaemia in paediatric patients receiving denosumab and after treatment discontinuation | Routine risk communication:<br><br>SmPC sections 4.2, 4.4 and 4.8.<br><br>PIL section 2.<br><br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br><br>None<br><br>Other routine risk minimisation measures beyond the Product Information:<br><br>Legal status: Restricted medical prescription. |
| Fracture healing complications | Routine risk communication: |

| | |
|---|---|
| | SmPC section 5.3<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>None<br>Other routine risk minimisation measures beyond the Product Information:<br>Legal status: Restricted medical prescription. |
| Infection | Routine risk communication:<br>SmPC section 4.8.<br>PIL section 4.<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>None<br>Other routine risk minimisation measures beyond the Product Information:<br>Legal status: Restricted medical prescription. |
| Cardiovascular events | Routine risk communication:<br>None<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>None.<br>Other routine risk minimisation measures beyond the Product Information:<br>Legal status: Restricted medical prescription. |
| Malignancy | Routine risk communication:<br>None<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>None.<br>Other routine risk minimisation measures beyond the Product Information:<br>Legal status: Restricted medical prescription. |

# V.2. Additional Risk Minimisation Measures

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

- Osteonecrosis of the jaw

**Patient reminder card**

| | |
|---|---|
| Objectives | The objective for the patient reminder card is to provide information regarding the important identified risk: osteonecrosis of the jaw. |
| Rationale for the additional risk minimization activity | The purpose of the patient reminder card is to remind patients about important safety information that they need to be aware of before and during treatment with denosumab (Kefdensis) injections for osteoporosis and bone loss, including:<br>• the risk of osteonecrosis of the jaw during treatment with Kefdensis;<br>• the need to highlight any problems with their mouth or teeth to their doctors/nurses before starting treatment;<br>• the need to ensure good oral hygiene during treatment;<br>• the need to inform their dentist of treatment with Kefdensisand 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.<br>The patient reminder card will be given by prescribers to patients. |
| Plans to evaluate the effectiveness of the interventions and criteria for success | Monitor and evaluate post-marketing and clinical study safety data and report in periodic safety update reports (PSURs). |
| Evaluation of the effectiveness of risk minimization activities | Routine pharmacovigilance activities will be performed to identify new safety signals and monitor reporting trends. |

EU = European Union; ONJ =osteonecrosis of the jaw; PSUR = periodic safety update report

# V.3 Summary of risk minimisation measures

| Safety concern | Routine risk minimisation activities | Pharmacovigilance activities |
|---|---|---|
| Hypocalcaemia | Routine risk minimisation measures:<br><br>SmPC sections 4.2, 4.3, 4.4 and 4.8.<br><br>PIL sections 2 and 4.<br><br>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.<br><br>In order to inform patients of this risk, corresponding text is also present in the PIL sections 2 and 4.<br><br>Legal status: Restricted medical prescription.<br><br>Additional risk minimisation measures:<br><br>None. | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br><br>Specific follow-up questionnaire.<br><br>Additional pharmacovigilance activities:<br><br>None. |
| Skin infection leading to hospitalisation | Routine risk minimisation measures:<br><br>SmPC sections 4.4 and 4.8.<br><br>PIL sections 2 and 4.<br><br>Legal status: Restricted medical prescription.<br><br>Additional risk minimisation measures:<br><br>None. | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br><br>Specific follow-up questionnaire<br><br>Additional pharmacovigilance activities:<br><br>None. |

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

| Safety concern | Routine risk minimisation activities | Pharmacovigilance activities |
|---|---|---|
| | groin pain is included in SmPC Section 4.4.<br><br>In order to inform patients of this risk, corresponding text is also present in the PIL sections 2 and 4.<br><br>Legal status: Restricted medical prescription.<br><br>Additional risk minimisation measures:<br><br>None. | reactions reporting and signal detection:<br><br>Specific follow-up questionnaire.<br><br>Additional pharmacovigilance activities:<br><br>None. |
| Hypercalcaemia in paediatric patients receiving denosumab and after treatment discontinuation | Routine risk minimisation measures:<br><br>SmPC sections 4.2, 4.4 and 4.8.<br><br>PIL section 2.<br><br>Legal status: Restricted medical prescription.<br><br>Additional risk minimisation measures:<br><br>None. | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br><br>None.<br><br>Additional pharmacovigilance activities:<br><br>None. |
| Fracture healing complications | Routine risk minimisation measures:<br><br>SmPC section 5.3<br><br>Legal status: Restricted medical prescription.<br><br>Additional risk minimisation measures:<br><br>None. | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br><br>Specific follow-up questionnaire.<br><br>Additional pharmacovigilance activities:<br><br>None. |
| Infection | Routine risk minimisation measures:<br><br>SmPC section 4.8.<br><br>PIL section 4.<br><br>Legal status: Restricted medical prescription. | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br><br>Specific follow-up questionnaire.<br><br>Additional pharmacovigilance activities: |

| Safety concern | Routine risk minimisation activities | Pharmacovigilance activities |
|---|---|---|
| | Additional risk minimisation measures:<br><br>None. | None. |
| Cardiovascular events | Routine risk minimisation measures:<br><br>None.<br><br>Legal status: Restricted medical prescription.<br><br>Additional risk minimisation measures:<br><br>None. | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br><br>None.<br><br>Additional pharmacovigilance activities:<br><br>None. |
| Malignancy | Routine risk minimisation measures:<br><br>None.<br><br>Legal status: Restricted medical prescription.<br><br>Additional risk minimisation measures:<br><br>None. | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br><br>Specific follow-up questionnaire.<br><br>Additional pharmacovigilance activities:<br><br>None. |

# Part VI: Summary of the risk management plan

# Summary of RMP for Kefdensis 60 mg solution for injection in pre-filled syringe

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

Kefdensis's summaries of product characteristics (SmPCs) and their package leaflet give essential information to health care professionals and patients on how Kefdensis should be used.

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

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

## I. The medicine and what it is used for

Kefdensis 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, Kefdensis significantly reduces the risk of vertebral, non-vertebral and hip fractures; treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. In men with prostate cancer receiving hormone ablation, Kefdensis significantly reduces the risk of vertebral fractures; and treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture. It contains denosumab as the active substance and it is given by the subcutaneous route of administration.

Further information about the evaluation of Kefdensis's benefits can be found in Kefdensis's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: (link to the EPAR summary landing page).

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

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

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

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals ;
- Important advice on the medicine's packaging;
- The 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 addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

## II.A List of important risks and missing information

Important risks of Kefdensis are risks that need special risk management activities to further investigate or minimize 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 Kefdensis. 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<br>Skin infection leading to hospitalisation<br>Osteonecrosis of the jaw<br>Hypersensitivity reactions<br>Atypical femoral fracture<br>Hypercalcaemia in paediatric patients receiving denosumab and after treatment discontinuation |
| Important potential risks | Fracture healing complications<br>Infection<br>Cardiovascular events<br>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, PTH resistance, vitamin D deficiency or resistance, thyroid surgery, parathyroid surgery, malabsorption syndromes, exCIsion of small intestine, severe renal impairment (CrCL < 30 mL/min), dialysis, and some medications (Finkelstein, 2001). |
| Risk minimisation measures | Routine risk minimisation measures: |

| **Important identified risk: Hypocalcaemia** | |
|---|---|
| | SmPC sections 4.2, 4.3, 4.4 and 4.8.<br><br>PIL sections 2 and 4.<br><br>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.<br><br>In order to inform patients of this risk, corresponding text is also present in the PIL sections 2 and 4.<br><br>Legal status: Restricted medical prescription.<br><br>Additional risk minimisation measures:<br><br>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, HIV/acquired immune deficiency syndrome (AIDS), immunosuppressant drugs (eg, 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:<br><br>SmPC sections 4.4 and 4.8.<br><br>PIL sections 2 and 4.<br><br>Legal status: Restricted medical prescription.<br><br>Additional risk minimisation measures:<br><br>None. |

| **Important identified risk: Osteonecrosis of the Jaw** | |
|---|---|
| Evidence for linking the risk to the medicine | Osteonecrosis of the Jaw have been observed in the clinical trial program of the originator. |
| Risk factors and risk groups | Risk factors include duration of exposure to denosumab, prior bisphosphonate use (particularly for extended periods of time), older |

| **Important identified risk: Osteonecrosis of the Jaw** | |
|---|---|
| | age, periodontal disease, dentoalveolar surgery, trauma from poorly fitting dentures, malignancy, chemotherapy, corticosteroids, smoking, systemic or regional infection, immune-compromised state predisposing to increased risk of infection, hypercoagulable state secondary to underlying malignancy, and vascular insufficiency due to thrombosis (Mehrotra and Ruggiero, 2006; Ruggiero et al, 2006). |
| Risk minimisation measures | Routine risk minimisation measures:<br>SmPC sections 4.4 and 4.8.<br>PIL sections 2 and 4.<br>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.<br>In order to inform patients of this risk, corresponding text is also present in the PIL sections 2 and 4.<br>Legal status: Restricted medical prescription.<br>Additional risk minimisation measures:<br>Patient reminder card |

| **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:<br>SmPC sections 4.3 and 4.8.<br>PIL sections 2 and 4.<br>Legal status: Restricted medical prescription.<br>Additional risk minimisation measures:<br>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 AFF. Corticosteroids have also been reported in the literature to potentially be associated with AFF (Meier et al, 2012; Giusti et al, 2011). Atypical femoral fractures have also been reported in patients with certain comorbid conditions (eg, vitamin D deficiency, RA, hypophosphatasia) and with use of bisphosphonates, glucocorticoids, and proton pump inhibitors (Shane et al, 2010). |
| Risk minimisation measures | Routine risk minimisation measures:<br>SmPC sections 4.4 and 4.8.<br>PIL sections 2 and 4.<br>Recommendation for reporting new or unusual thigh, hip, or groin pain is included in SmPC Section 4.4.<br>In order to inform patients of this risk, corresponding text is also present in the PIL sections 2 and 4.<br>Legal status: Restricted medical prescription.<br>Additional risk minimisation measures:<br>None. |

| **Important identified risk: Hypercalcaemia 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 OI). |
| Risk minimisation measures | Routine risk minimisation measures:<br>SmPC sections 4.2, 4.4 and 4.8.<br>PIL section 2.<br>Legal status: Restricted medical prescription.<br>Additional risk minimisation measures: |

| **Important identified risk: Hypercalcaemia in paediatric patients receiving denosumab and after treatment discontinuation** | |
|---|---|
| | None. |

| **Important potential risk: Fracture healing complications** | |
|---|---|
| Evidence for linking the risk to the medicine | This is a theoretical risk based on the mechanism of action. |
| Risk factors and risk groups | General risk factors for fracture healing complications are thought to include older age, diabetes, use of medications such as non-steroidal anti-inflammatory drugs and corticosteroids, smoking, excessive alcohol use, and poor nutrition (Hernandez et al, 2012; Gaston and Simpson, 2007). |
| Risk minimisation measures | Routine risk minimisation measures:<br>SmPC section 5.3<br>Legal status: Restricted medical prescription.<br>Additional risk minimisation measures:<br>None. |

| **Important potential risk: Infection** | |
|---|---|
| Evidence for linking the risk to the medicine | This is considered a potential risk based on theoretical concerns which have not been substantiated in the extensive clinical study program or in the postmarketing experience. |
| Risk factors and risk groups | Risk factors for infection in general include increasing age, immunosuppression associated with cancer, diabetes, HIV/AIDS, immunosuppressant drugs (eg, corticosteroids, arthritis medications, and chemotherapy drugs), substance abuse, and malnutrition. |
| Risk minimisation measures | Routine risk minimisation measures:<br>SmPC section 4.8.<br>PIL section 4.<br>Legal status: Restricted medical prescription.<br>Additional risk minimisation measures:<br>None. |

| **Important potential risk: Cardiovascular events** | |
|---|---|
| Evidence for linking the risk to the medicine | This is a theoretical risk based on epidemiological data demonstrating elevated osteoprotegerin in patients with cardiovascular disease. |
| Risk factors and risk groups | The denosumab development program comprises studies of older subject populations (eg, osteoporosis, cancer) that are likely to have a higher incidence of pre-existing cardiovascular conditions and, thus, a higher incidence of cardiovascular toxicities than that of the general population (Schulz et al, 2004; Hak et al, 2000). Risk factors for atherosclerosis include age, sex, ethnicity, family history, elevated lipid levels, cigarette smoking, hypertension, diabetes, and concomitant medications, including antipsychotic agents and COX-2 inhibitors (Murphy and Dargie, 2007; Smith et al, 2004 ). |
| Risk minimisation measures | Routine risk minimisation measures:<br>None.<br>Legal status: Restricted medical prescription.<br>Additional risk minimisation measures:<br>None. |

| **Important potential risk: Malignancy** | |
|---|---|
| Evidence for linking the risk to the medicine | This is considered a potential risk based on theoretical concerns and has not been substantiated in the extensive clinical study program or in the post-marketing experience of the originator. |
| Risk factors and risk groups | General factors for risk of malignancy include advancing age, diet, cigarette smoking, excessive ethanol consumption, and numerous environmental toxins. In addition, cancer populations are at increased risk for a second primary malignancy because of their existing malignancy, possible genetic predisposition, and exposure to chemotherapy and radiation treatment (Anand et al, 2008; World Health Organization [WHO], 2010). |
| Risk minimisation measures | Routine risk minimisation measures:<br>None.<br>Legal status: Restricted medical prescription.<br>Additional risk minimisation measures:<br>None. |

## II.C Post-authorisation development plan

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

There are no studies that are conditions of the marketing authorisation or specific obligations of Kefdensis.

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

There are no studies required for Kefdensis.

# Part VII: Annexes

## Table of contents

# Annex 4 - Specific adverse drug reaction follow-up forms

## Table of Content

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

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

| Follow-up Form Title |
|---|
| Hypocalcemia |
| Infection |
| Osteonecrosis of the jaw |
| Potential atypical fracture |
| Fracture healing |
| Malignancy |
| Hypersensitivity |

**DENOSUMAB - Specific Adverse Reaction Follow-up Questionnaire**

**Hypocalcemia**

## 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 Trail

☐ 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)

☐ Numbness
(Specify if involving digits and/peri-oral region) _____

☐ Convulsions ☐ Muscle twitching

☐ Muscle cramping ☐ Paresthesia

☐ Syncope ☐ Tetany

☐ None ☐ Other _____

## DIAGNOSIS (Check all that apply)

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 ionized 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

## 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** _____

**DENOSUMAB - Specific Adverse Reaction Follow-up Questionnaire**

**Hypocalcemia (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 _____

**Hypocalcemic 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

Event Reported Term

Age at time of event: _____

Study No.

☐ Clinical Trail

☐ 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 _____

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

| Diagnostic | Results/Units | Reference range/Units | Date | Report Attached | |
|---|---|---|---|---|---|
| | | | | Y | N |
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| Diagnostic | Results/Units | Reference range/Units | Date | Report Attached | |
|---|---|---|---|---|---|
| | | | | Y | N |
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**DENOSUMAB - Specific Adverse Reaction Follow-up Questionnaire**

**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 _____
- ☐ 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: _____

☐ Wound and skin infections

- ☐ Cellulitis _____
- ☐ Erysipelas _____
- ☐ Necrotizing fasciitis _____
- ☐ Abscess _____
- ☐ Other skin infections, please specify: _____

☐ Opportunistic infections

- ☐ Aspergillus (invasive forms only) _____
- ☐ Blastomycosis pulmonary or extra-pulmonary infections _____
- ☐ Candidiasis systemic_____
- ☐ Coccidioidemycosis secondary/systemic_____
- ☐ Cryptococcal infection-pulmonary and non-pulmonary_____
- ☐ Cytomegalovirus-include systemic site _____
- ☐ Herpes simplex (meningitis or encephalitis) _____
- ☐ Herpes zoster (only systemic or disseminated: involving 2 or more dermatomes) _____
- ☐ Histoplasma infections - chronic disseminated or severe acute _____
- ☐ Mucormycosis (=zygomycosis) including infections due to Rhizopus, Mucor and Absidia of lung, genito-urinary tract, kidney, GIT, skin _____
- ☐ Mycobacterium tuberculosis _____
- ☐ Non-tuberculosis mycobacterium _____
- ☐ Nocardia infection - of brain, lungs, kidney, skin _____
- ☐ Paracoccidioides infections of lungs, skin other _____
- ☐ Pneumocystis carinii pneumonia_____
- ☐ Sporotrichosis - disseminated infections _____
- ☐ Toxoplasmosis encephalitis or disseminated _____
- ☐ Other opportunistic infections, please specify: _____

**DENOSUMAB - Specific Adverse Reaction Follow-up Questionnaire**

**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.) _____

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**

**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:_____

☐Synovial 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_____

## 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

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

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

☐Chronic lung disease_____

☐Hepatitis_____

☐Chronic kidney disease_____

☐Liver disease_____

☐ Congenital infections/malformations____

☐Osteomyelitis_____

☐HIV_____

☐Diabetes mellitus_____

☐Cancer (specify)_____

☐Recent wounds/infections_____

☐Immunosuppression_____

☐Known exposure to TNF inhibitors__

☐Chemotherapy

☐Malnutrition/failure to thrive_____

☐Exposure to infectious agents_____

☐ Personal contact___ Body fluids___

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

☐ Potentially contaminated food/liquid____

Report to
Email:

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

**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.

☐ Clinical Trail

☐ 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

_____

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

Visible evidence of exposed bone, or bone that can be probed through an intraoral or extraoral fistula(e) in the maxillofacial region:

☐ No ☐ Yes ☐ Unknown; Please describe _____

_____

Date exposed bone was first visualized/probed: _____

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

☐ No ☐ Yes ☐Unknown _____

Prior history of radiation therapy to jaw:

☐ No ☐ Yes ☐Unknown_____

Prior history of metastatic disease to jaw:

☐ No ☐ Yes ☐Unknown

Describe _____

_____

Please indicate the location of involved area(s)

Please describe location(s)

☐ Right maxilla, teeth and lateral jaw

☐ Left maxilla, teeth and lateral jaw

☐ Right maxilla, medial jaw

☐ Left maxilla, medial jaw

☐ Right mandible teeth and lateral jaw

☐ Left mandible teeth and lateral jaw

☐ Right mandible, medial jaw

☐ Left mandible, medial jaw

☐ Maxilla hard palate

☐ Other (specify) _____

Report to

Email:

**Oral Findings**

Evidence of infection: ☐ No ☐ Yes ☐ Unknown

Please describe _____

Exposed bone at the site of extraction

☐ No ☐ Yes ☐ Unknown

Complete coverage of involved area(s) by mucosa

☐ No ☐ Yes ☐ Unknown

If yes, date of complete mucosal coverage _____

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

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

Please describe the clinical signs/symptoms/location:

_____

_____

_____

_____

**REPORTER**

Name:

Address:

City: State/

Country: Province:

Email: Postal code:

Phone (include country code)

**Signature** _____

**Title** _____ **Date** _____

**DENOSUMAB - Specific Adverse Reaction Follow-up Questionnaire**

**Osteonecrosis of the Jaw (Continued)**

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

| Patient Identifier | Patient Initials | Safety Database No. |
|---|---|---|
| | | |

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

Dental/Oral surgery/stomatology consultations ☐No ☐Yes ☐Unknown If yes please give date of examination _____

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

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

Antibiotics ☐No ☐Yes ☐Unknown If yes, agent(s)/route/dose_____ Start Date _____ Stop Date_____

Please describe outcomes of the treatment_____

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

Please describe outcomes of the treatment_____

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

Start Date _____ Stop Date_____

Please describe outcomes of the treatment_____

Hospitalizations ☐ No ☐ Yes ☐ Unknown If yes, reason for hospitalization _____

Hospitalization begin date _____ Hospitalization end date _____

Please describe outcomes of treatment_____

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

History of poor oral hygiene ☐ No ☐ Yes ☐ Unknown _____

Dental extraction recently ☐ No ☐ Yes ☐ Unknown If yes, date of procedure _____

Dental surgery recently ☐ No ☐ Yes ☐ Unknown If yes, date of procedure _____

Periodontal disease including gingival bleeding, calculus, etc ☐ No ☐ Yes ☐ Unknown Start date _____ Stop date _____

Draining fistula in affected area ☐ No ☐ Yes ☐ Unknown Start date _____ Stop date _____

Dental abscess in affected area ☐ No ☐ Yes ☐ Unknown Start date _____ Stop date _____

Osteomyelitis in affected area ☐ No ☐ Yes ☐ Unknown Start date _____ Stop date _____

Root-canal treatment near affected area ☐ No ☐ Yes ☐ Unknown If yes, date of treatment _____

Dental treatment, surgery or tooth extraction to the involved area within last 4-6 months PRIOR to the onset of the oral lesion ☐ No ☐ Yes ☐ Unknown

History of dentures /dental appliance / implant ☐ No ☐ Yes ☐ Unknown If yes, please specify ☐ upper ☐ lower

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

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

PO bisphosphonate ☐ No ☐ Yes ☐ Unknown

If yes, agent(s)/dose_____

Start date _____ Stop date _____

IV bisphosphonate ☐ No ☐ Yes ☐ Unknown If yes, agent(s)/dose_____

Start date _____ Stop date _____

Glucocorticoid use within the past 12 months ☐ No ☐ Yes ☐ Unknown If yes, agent(s)/dose _____

Start date _____ Stop date _____

Immunosuppressant use within the past 12 months ☐ No ☐ Yes ☐ Unknown If yes, agent(s)/dose _____

Start date _____ Stop date _____

Chemotherapy within the past 12 months ☐ No ☐ Yes ☐ Unknown If yes, agent(s)/dose_____

Start date _____ Stop date _____

Anti-angiogenic agents (e.g. bevacizumab) within the past 12 months ☐ No ☐ Yes ☐ Unknown If yes, agent(s)/dose_____

Start date _____ Stop date _____

## OTHER 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

## Patient Reminder Card Status (for EU Patients)

Received a patient reminder card prior to the ONJ event:

☐ Yes ☐ No ☐ Unknown

_____

_____

Report to

Email:

**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

## 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 beaking 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

**DENOSUMAB - Specific Adverse Reaction Follow-up Questionnaire**

**Potential Atypical Fracture (Continued)**

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

| Patient Identifier | Patient Initials | Date of This Report |
|---|---|---|
| | | |

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

Methods to reduce and set fracture:

☐ Non-surgical reduction_____

☐ Casting_____

☐ Surgery _____

☐ Revision surgery (2nd surgery) _____

☐ Other_____

_____

☐ Unknown_____

_____

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

General:

☐ History or current corticosteroid use

☐ Affected hip with prior surgical pinning

☐ Affected hip with prior hip replacement

Cancer:

Evidence of any metastases: ☐Yes ☐No ☐Unknown

If yes, did metastases involve bone? ☐Yes ☐No ☐Unknown

Metastasis in femur where fracture occurred?

☐Yes ☐No ☐Unknown

Prior osteoporosis therapy:

☐ Estrogen

☐ Selective estrogen receptor modulator (SERM)

☐ Bisphosphonate (please indicate)

☐ Intravenous ☐ Oral

If yes, how long has therapy been received? (months, years) _____

☐ Parathyroid hormone

Past medical and surgical history: _____

_____

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

Event Reported Term

Age at time of event: _____

Study No.

Safety Database No.

☐ Clinical Trail

☐ 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) _____(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
☐ Hip
☐ Patella
☐ Pelvis
☐ Tibia
☐ Fibula

☐ Foot/tarsal/metatarsal/phalange

☐ Other_____

_____

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

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

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

☐ Non-traumatic

**Characteristics of fracture (check all that apply):**

☐ Comminuted
☐ Compound
☐ Pathologic
☐ Poor alignment
☐ Poor immobilization of segments
☐ Soft tissue injury
☐ Unknown

**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

_____
_____
_____
_____

**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**

**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 ☐

**TREATMENT:**

Hospitalized? Yes ☐ No ☐ Unknown ☐

ICU admission? Yes ☐ No ☐ Unknown ☐

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

Surgical treatment? Yes ☐ No ☐ Unknown ☐

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

Hormonal treatment? Yes ☐ No ☐ Unknown ☐

Radiation treatment? Yes ☐ No ☐ Unknown ☐

Bone marrow transplant? Yes ☐ No ☐ Unknown ☐

If yes, autologous ☐ heterologous ☐

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

**RISK FACTORS (Check all that apply):**

Smoking ☐

Prior Malignancy ☐

Positive Family History (Check all that apply):

Same cancer ☐

Different cancer ☐

Prior therapeutic radiation exposure ☐

Environmental exposure ☐

Specify:_____

**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 Trail

☐ 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 | _____ |

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

**Key messages of the additional risk minimization measures**

**Patient reminder card:**

Patient Reminder Cards for osteonecrosis of the jaw (ONJ) are available to prescribers of Kefdensis.

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

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