GEDEON RICHTER PLC.

RISK MANAGEMENT PLAN

FOR

Junod 60 mg solution for injection in pre-filled syringe

EU Risk Management Plan for Junod (denosumab)

RMP version to be assessed as part of this application:

RMP Version number	0.2
Data lock point for this RMP:	24 April 2024
Rationale for submitting an updated RMP	Not applicable
Summary of significant changes in this RMP	Not applicable

QPPV name	**Attila Oláh MD**
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Date of final sign off	Please see e-signature page at the end of the document

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Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) (INN or common name)	denosumab
Pharmacotherapeutic group(s) (ATC Code)	Drugs for treatment of bone diseases – Other drugs affecting bone structure and mineralisation (M05BX04)
Marketing Authorisation Applicant	Gedeon Richter Plc.
Medicinal products to which this RMP refers	#1
Invented name(s) in the European Economic Area (EEA)	Junod
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Junod is a human monoclonal antibody of the immunoglobulin G2 subclass, biosimilar to the licensed denosumab, Prolia, the reference product.
	Summary of mode of action: Denosumab targets and binds with high affinity and specificity to human receptor activator of nuclear factor kappa-B (RANK) 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: Denosumab is produced in a mammalian cell line (Chinese hamster ovary cells) by recombinant DNA technology.
Hyperlink to the Product Information	Please see eCTD Module 1.3.1.
Indication(s) in the EEA	Current: Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures. Junod 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, Junod significantly reduces the risk of vertebral fractures. 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: 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): 60 mg solution for injection in pre-filled syringe
	Proposed (if applicable): not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

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

According to the Guideline on good pharmacovigilance practices (GVP) Module V (EMA/838713/2011 Rev 2) this part of the RMP could be omitted.

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

In line with the current regulatory guiding principles of both EMA (Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues- EMEA/CHMP/BMWP/42832/2005 Rev1 and Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues- EMA/CHMP/BMWP/403543/2010) and FDA (Scientific Considerations in Demonstrating Biosimilarity to a Reference Product, 2015) and following the EMA, FDA, and national (Paul Ehrlich Institute) regulatory interactions (EMA 2019, EMA 2020, FDA 2019, FDA 2020, PEI 2018), comparative *in vivo* pharmacokinetic and toxicological studies of the biosimilar denosumab (RGB-14-P / RGB-14-X) and their respective reference products, Prolia / Xgeva have not been performed.

Part II: Module SIII - Clinical trial exposure

The biosimilar comparability programme contained a Phase I comparative pharmacokinetic clinical trial conducted in healthy subjects (RGB-14-001) and a Phase III comparative clinical efficacy and safety trial conducted in subjects with post-menopausal osteoporosis (RGB-14-101), against the reference products, Xgeva (in Phase I) and Prolia (in Phase III), respectively.

In these completed clinical trials, 325 subjects have been exposed to RGB-14 (denosumab) (see Table SIII.1). All these subjects were exposed to RGB-14 60 mg. Apart from 325 subjects, there were additional 62 subjects who received two doses of Prolia and then received RGB-14(-P) 60 mg. Of note, these 62 subjects were not added to the total number of 325 subjects exposed to RGB-14.

Table SIII.2, SIII.3 and SIII.4 show cumulative subject exposure by sex, product, age range, by race and by treatment duration.

Table SIII.1 – Cumulative subject exposure from clinical trials

Treatment	Number of subjects
RGB-14	**325**
RGB-14-P	242
RGB-14-X*	83
Active comparators	**313**
Prolia	231
Xgeva*	82

**60 mg subcutaneous injection was administered*

Table SIII.2 - Cumulative subject exposure to investigational drug from completed clinical trials by sex, product and age range

Sex **Product** **Age range**	**Number of subjects**
Male	
RGB-14-X*	
28-34 years	31
35-55 years	52
Female	
RGB-14-P	
60-64 years	100
65-83 years	142
Total	**325**

**60 mg subcutaneous injection was administered*

Table SIII.3 - Cumulative subject exposure to investigational drug from completed trials by race

Race	Number of subjects
White	306
Black	2
Asian	2
Other	15
Total	**325**

Table SIII.4 - Subject exposure in clinical trials by treatment duration

Exposure	Medicinal product		Total
	RGB-14-P	RGB-14-X*	
1 dose of 60 mg	242[a]	83	325
2nd dose	227	0	227
3rd dose	63	0	63

**60 mg subcutaneous injection was administered*

[a] In addition, among subjects who completed the Main Period (52 weeks) in study RGB-14-101, 62 subjects who received two doses of Prolia were transitioned to receive RGB-14-P as the third dose.

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

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

Criteria: **Hypocalcaemia (albumin adjusted serum calcium <2.1 mmol/L (8.4 mg/dL)) or hypercalcaemia (>2.62 mmol/L (10.6 mg/dL))**
Reason for exclusion: To avoid confounding the evaluation of safety.
Included as missing information?: No
Rationale: Hypocalcaemia is contraindicated in the Summary of Product Characteristics (SmPC). Pre-existing hypocalcaemia must be corrected prior to initiating therapy.

Criteria: **Vitamin D deficiency (serum 25 hydroxyvitamin D level <50 nmol/L (20 ng/mL))**
Reason for exclusion: Vitamin D is essential in the regulation of calcium homeostasis and bone health.
Included as missing information?: No
Rationale: As per the SmPC, patients must be adequately supplemented with vitamin D.

Criteria: **Infection**
Reason for exclusion: Standard exclusion criteria to avoid confounding the evaluation of safety: Active infection (including, but not limited to SARS-CoV-2, hepatitis B/hepatitis B surface antigen (HbsAg) positivity and/or participant who had anti hepatitis B core antibody (HbcAb) positivity with anti-HbsAb negativity, hepatitis C and human immunodeficiency virus infections) and subjects presented with clinically significant leukopenia, neutropenia or anaemia.
Included as missing information?: No
Rationale: It is an important risk of denosumab treatment.

Criteria: **Uncontrolled hypothyroidism or hyperthyroidism, history and/or presence of hypoparathyroidism or hyperparathyroidism**
Reason for exclusion: To avoid confounding the evaluation of safety and efficacy endpoints.
Included as missing information?: No
Rationale: Thyroid hormones are essential for normal skeletal development and normal bone metabolism.

Criteria: **History and/or presence of bone metastases, renal osteodystrophy, osteomyelitis, certain bone diseases, history of malignancy within 5 years before screening**
Reason for exclusion: The above detailed conditions (examples for excluded bone diseases: Paget's disease, rheumatoid arthritis, Cushing's disease) would confound the evaluation of safety and possible efficacy endpoints.
Included as missing information?: No
Rationale: As per the SmPC, patients should be monitored for radiological signs of malignancy, new radiolucency or osteolysis.

Criteria: **Known history of hypersensitivity to monoclonal antibodies or to any components of the solution for injection formulation**
Reason for exclusion: To avoid hypersensitivity reactions and confounding evaluation of safety.
Included as missing information?: No
Rationale: Use of denosumab is contraindicated in case of hypersensitivity to the active substance or to any excipients of the formulation.

Criteria: **Pregnant, lactating or planning to become pregnant during the study period and for 5 months after final study treatment administration**
Reason for exclusion: a standard exclusion in clinical trials to avoid exposure of pregnant women to investigational medicinal products. In addition, denosumab bears the potential risk to the foetus. It is not known whether denosumab is transferred into human milk.
Included as missing information?: No
Rationale: These populations are not included into the intended indications. Risk minimisation via product labelling instructing patients to avoid pregnancy and breastfeeding is in place.

Criteria: **History and/or presence of certain fractures: hip fracture, atypical femoral fracture or certain vertebral fractures, additionally active healing fractures at the time of screening**
Reason for exclusion: To avoid confounding the evaluation of safety and efficacy endpoints.
Included as missing information?: No
Rationale: Denosumab 60 mg aim to treat osteoporosis and/or bone loss in patients at increased risk of fracture, denosumab 120 mg aims to prevent skeletal related events, such as pathological fracture. Atypical femoral fracture is an important risk of denosumab treatment.

Criteria: **Use of concomitant medications affecting bone health**
Reason for exclusion: Subjects with previous or current osteoporosis therapy (e.g., denosumab, romosozumab, strontium, bisphosphonates, teriparatide, abaloparatide) and subjects requiring on-going use of any osteoporosis treatment and/or subjects with previous or current therapy affecting bone health (e.g., tibolone, oestrogen, antioestrogen, selective oestrogen receptor modulators (SERMs), aromatase inhibitors, calcitonin and its derivatives, other calcimimetics, systemic glucocorticoids, heparin, vitamin K) would confound the evaluation of efficacy endpoints.
Included as missing information?: No
Rationale: As per the SmPC, no clinically relevant alterations are expected in trough serum concentration and pharmacodynamics of denosumab (creatinine adjusted urinary N-telopeptide, uNTX/Cr) by concomitant chemotherapy and/or hormone therapy or by previous intravenous bisphosphonate exposure. Patients should not be treated concomitantly with bisphosphonates.

Criteria: **History and/or presence of osteonecrosis of the jaw (ONJ) or of the external auditory canal**
Reason for exclusion: ONJ is a known risk of denosumab treatment. Subjects with history and/or presence of ONJ or osteonecrosis of the external auditory canal, or risk factors for ONJ (e.g., smoking, invasive dental procedures without complete healing or planned during the study period, planned radiotherapy to the head and neck, poor oral hygiene) were excluded to avoid confounding evaluation of safety.
Included as missing information?: No
Rationale: Risk minimisation via product labelling informing patients about the risk of developing ONJ is in place.

Criteria: **Inadequate renal and hepatic function**
Reason for exclusion: To have a clean and consistent population to facilitate evaluation of efficacy and safety of denosumab, subjects who are on dialysis or their estimated glomerular filtration rate (eGFR) is <30 mL/min, serum alanine aminotransferase is ≥ 2xULN or serum aspartate aminotransferase is ≥ 2xULN or total bilirubin ≥ 1.5×ULN (except in Gilbert's syndrome, where the total bilirubin was accepted if ≤ 2.5 × ULN) were excluded.
Included as missing information?: No

Rationale: As per the SmPC, the pharmacokinetics of denosumab is not expected to be affected by renal or hepatic impairment. Monitoring of calcium levels and adequate intake of calcium and vitamin D is especially important in patients with renal impairment.

Criteria: **History and/or presence of significant cardiac disease or ECG abnormalities**
Reason for exclusion: This would indicate significant risk for participating in the study and might result in the subject discontinuing the study.
Included as missing information?: No
Rationale: Based on single and repeated dose toxicity studies, no impact on cardiovascular physiology is expected.

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	0
Breastfeeding women	
Patients with relevant comorbidities: Patients with hepatic impairment Patients with renal impairment Patients with cardiovascular impairment Immunocompromised patients Patients with a disease severity different from inclusion criteria in clinical trials	0
Population with relevant different ethnic origin	Among 325 subjects from completed clinical trials: White: 94.2% Black: 0.6% Asian: 0.6% Other: 4.6%
Subpopulations carrying relevant genetic polymorphisms	0
Other Paediatric patients Geriatric patients	0 65–70-year-olds: 25.5% 71-75-year-olds: 12.9% 76-80-year-olds: 4.3% >81-year-olds: 0.9%

Part II: Module SV - Post-authorisation experience

Not applicable.

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

Potential for misuse for illegal purposes
There is no apparent potential for misuse of RGB-14 for illegal purposes.

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

This category has not been determined by the initial RMP.

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

Junod 60 mg solution for injection in pre-filled syringe (Gedeon Richter Plc.) has demonstrated to be a biosimilar medicine to the reference product Prolia 60 mg solution for injection in pre-filled syringe (Amgen Europe B.V.) which has been authorised in the EU since 26 May 2010.

The safety concern list for Junod has been based on the European Risk Management Plan (v31.0, date: 11 January 2023) of the reference medicinal product, Prolia (MAH: Amgen). All important risks relevant for risk management were harmonised with those of Prolia regardless of no proposed additional pharmacovigilance activities.

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

Not applicable.

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

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

Important identified risk: Hypocalcaemia

Potential mechanisms:
Denosumab inhibits osteoclast bone resorption, thereby decreasing the release of calcium from bone into the bloodstream.

Evidence source(s) and strength of evidence:
This risk was identified in the phase III, randomised, double-blind, placebo- or active-controlled studies of the reference product.

Characterisation of the risk:
Frequency: In two phase III placebo-controlled clinical trials with the reference product in post-menopausal women with osteoporosis, approximately 0.05% of subjects had declines of serum calcium levels (less than 1.88 mmol/L) following denosumab administration. In two phase III placebo-controlled clinical trials in subjects receiving hormone ablation or in the phase III placebo-controlled clinical trial in men with osteoporosis, no declines of serum calcium levels (less than 1.88 mmol/L) were observed.

No serum calcium level decline below 1.88 mmol/L were observed in clinical trials with RGB-14.

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

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

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

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

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

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 the therapy in all patients receiving denosumab. Monitoring of calcium levels is recommended during treatment, especially in those with renal impairment.

Impact on the risk-benefit balance of the product:
A severe hypocalcaemia can cause life-threatening complications such as seizures and congestive heart failure. Routine risk minimisation measures and routine pharmacovigilance activities further characterise the risk of hypocalcaemia.

Public health impact:
Significant public health impact is not expected as this risk is preventable and treatable with the appropriate risk minimisation measures.

Important identified risk: Skin infection leading to hospitalisation

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

Evidence source(s) and strength of evidence:
This risk was identified in the phase III, randomised, double-blind, placebo- or active-controlled studies with the reference product.

Characterisation of the risk:
Frequency: In phase III placebo-controlled clinical trials with the reference product, the overall frequency of skin infections was similar between the placebo and the denosumab groups: in post-menopausal women with osteoporosis (placebo [1.2%] versus denosumab [1.5%]); in men with osteoporosis (placebo [0.8%] versus denosumab [0%); in breast or prostate cancer patients

receiving hormone ablation (placebo [1.7%] versus denosumab [1.4%). Skin infections leading to hospitalisation were reported in 0.1% of post-menopausal women with osteoporosis receiving placebo versus 0.4% denosumab. These cases were predominantly cellulitis. Skin infections reported as serious adverse reactions were similar in the placebo (0.6%) and the denosumab (0.6%) groups in the breast and prostate cancer studies.

No skin infections leading to hospitalisation were reported in clinical trials with RGB-14.

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

Reversibility: These events typically resolved with administration of antibiotics.

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

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

Risk factors and risk groups:
Risk factors for infection in general include increasing age, immunosuppression associated with cancer, diabetes, human immunodeficiency virus /acquired immune deficiency syndrome, 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:
Routine pharmacovigilance activities further characterise the risk of skin infection leading to hospitalisation.

Public health impact:
Minimal impact, as rare skin infections leading to hospitalisation can be effectively treated with antibiotics.

Important identified risk: Osteonecrosis of the jaw

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

Evidence source(s) and strength of evidence:
This risk was identified in open-label long-term extensions to phase III, randomised, double-blind, placebo-controlled studies with the reference product.

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

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

No ONJ was reported in clinical trials with RGB-14.

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

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

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

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

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

Preventability:
A dental examination with appropriate preventive dentistry is recommended prior to the treatment, 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 RGB-14, should receive care by a dentist or an oral surgeon. In patients who develop ONJ during the treatment, 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:
ONJ can lead to necrotic bone or fistula. Routine risk minimisation measures and routine pharmacovigilance activities further characterise the risk of ONJ.

Public health impact:
Significant public health impact is not expected due to the rarity of the risk. Routine risk minimisation measures and routine pharmacovigilance activities further characterise the risk of ONJ.

Important identified risk: 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 with the reference product.

Characterisation of the risk:
Frequency: In the pooled post-menopausal osteoporosis (PMO) / hormone ablation therapy (HALT) pivotal studies with the reference product, 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% Cl: 0.83,1.90). Subject incidence of potential clinical consequences of hypersensitivity was 1.3% in both treatment groups; HR = 0.94 (95% Cl: 0.66, 1.33). In the 24-month final analysis of the glucocorticoid-induced osteoporosis (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% Cl] = 1.41 [0.77, 2.59]).

No hypersensitivity reactions were reported in clinical trials with RGB-14.

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

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

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

Impact on quality of life: For severe hypersensitivity reactions, patients may be treated in the emergency room and/or 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 and any of its excipients.

Impact on the risk-benefit balance of the product:
Routine pharmacovigilance activities further characterise the risk of hypersensitivity reactions.

Public health impact:
No significant public health impact is expected due to the rarity of the risk.

Important identified risk: Atypical femoral fracture

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

Evidence source(s) and strength of evidence:
This risk was identified in an open-label long-term extension to a phase III, randomised, double-blind, active-controlled study with the reference product.

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

No AFF was reported in clinical trials with RGB-14.

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

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

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

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

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

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

Impact on the risk-benefit balance of the product:
The risk for complications of AFF may vary according to age, the anatomy of the fracture, and other medical conditions, e.g., people with low bone mass or diabetes may be at greater risk for some complications.
Public health impact:
No significant public health impact is expected due to the rarity of the risk.

Important identified risk: 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 modelling 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:
This risk was identified in clinical trials and from post-marketing setting with the reference product.

Characterisation of the risk:
Frequency: A phase III study with the reference product was conducted in children with osteogenesis imperfecta, aged 2 to 17 years, 52.3% male, 88.2% Caucasian. Subjects initially received up to a maximum of 60 mg, every 6 months for 36 months and 60 subjects transitioned to every 3 months dosing. Hypercalcaemia was reported during every 6 months (19%) and every 3 months (36.7%) dosing. The studies were terminated early due to the occurrence of life-threatening events and hospitalisations due to hypercalcaemia.

No paediatric subjects were included in clinical trials with RGB-14.

Severity: 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%).

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

Long-term outcomes: No long-term adverse effects are anticipated for properly treated hypercalcaemia.

Impact on quality of life: 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 (such as osteogenesis imperfecta).

Preventability:
No data are available on potential measures to prevent hypercalcaemia.

Impact on the risk-benefit balance of the product:
Routine pharmacovigilance activities further characterise the risk of hypercalcaemia in paediatric patients.

Public health impact:
No significant public health impact is expected.

Important potential risk: Fracture healing complications

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

Evidence source(s) and strength of evidence:
This is a theoretical risk based on the potential mechanism of action.

Characterisation of the risk:
Frequency: Of the subjects who had non-vertebral fractures in the large pivotal PMO study with the reference product, fracture healing complications (delayed healing or non-union) were reported in 2 of 386 subjects in the denosumab group (0.5%) and 5 of 465 subjects (1.1%) in the placebo group. Of the subjects who had non-vertebral fractures in the pivotal study for HALT-breast cancer, fracture healing complications were reported in 0 of 8 subjects in the denosumab group and 1 of 8 subjects (12.5%) in the placebo group. Because of the low incidence of fracture healing complications, 95% CIs were not calculated. No fracture healing complications were reported in the MOP study. No fracture healing complications were reported in the GIOP study.

No fracture healing complications were reported in clinical trials with RGB-14.

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

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

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

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

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

Preventability:
No preventive measures are known.

Impact on the risk-benefit balance of the product:
Complications of fractures may include osteomyelitis, malunions or delayed union and non-union fractures.

Public health impact:
No significant public health impact is expected.

Important potential risk: 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. No evidence of treatment effect of denosumab on immunoglobulin production was observed.

Evidence source(s) and strength of evidence:
This risk is considered based on theoretical concerns which has not been substantiated in the extensive clinical development programme or in the post-marketing experience of the reference product.

Characterisation of the risk:
Frequency: In the 24-month final analysis of the GIOP study with the reference product, 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% Cl] = 0.95 [0.54, 1.68]).

Events related to infection were reported in 48.2% of subjects receiving RGB-14-X and 42.7% of subjects receiving XGEVA, while in 39.3% of subjects receiving RGB-14-P and 38.5% of subjects receiving Prolia in clinical trial RGB-14-001 and RGB-14-101, respectively.

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

Reversibility: Infections when treated appropriately are generally reversible.

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

Impact on quality of life: For severe infection, patients may be 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 (e.g., corticosteroids, arthritis medications, and chemotherapy drugs), substance abuse, and malnutrition.

Preventability:
No preventive measures are known.

Impact on the risk-benefit balance of the product:
Early diagnosis and treatment may prevent complications such as bacteraemia, sepsis and septic shock, which are serious, life-threatening conditions that need immediate treatment. Routine and additional pharmacovigilance activities further characterise the risk of infections.

Public health impact:
No significant public health impact is expected.

Important potential risk: Cardiovascular events

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

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

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

During the placebo-controlled phase of the pivotal study for MOP, adverse events in the cardiac disorders system organ class (SOC) were reported in 8 (6.7%) denosumab-treated and 3 (2.5%) placebo-treated subjects (note: 2 events of angina tonsillitis in the denosumab group were incorrectly coded to the cardiac disorders adverse event category). The incidence of adverse events in the vascular disorders SOC was 5.0% in denosumab-treated and 6.7% in placebo-treated subjects.

In the GIOP study, adverse events in the cardiovascular disorders or vascular disorders SOC were reported in 65 (16.5%) denosumab-treated subjects and 53 (13.8%) risedronate-treated subjects (HR [95% Cl] = 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).

In clinical trials with RGB-14 cardiovascular events were reported with similar or lower frequency than with the reference product.

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

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

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

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

Risk factors and risk groups:

A higher incidence of pre-existing cardiovascular conditions and, thus, a higher incidence of cardiovascular toxicities is expected in elder patients than that in the general population (Schulz 2004; Hak 2000).

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

Preventability:
No preventive measures are known.

Impact on the risk-benefit balance of the product:
Cardiovascular diseases are the leading cause of death globally.

Public health impact:
No significant public health impact is expected.

Important potential risk: 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 tumour types provide no evidence for carcinogenic risk associated with RANKL inhibition (Armstrong 2008; Jones 2006; Mori 2007).

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

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

Evidence source(s) and strength of evidence:
This is considered a potential risk based on theoretical concerns and has not been substantiated in the extensive clinical development programme or in post-marketing setting with the reference product.

Characterisation of the risk:
Frequency: In the large pivotal PMO study (20030216) with the reference product, the subject incidence of new primary malignancy was 4.8% with denosumab and 4.3% with placebo (HR [95% Cl] = 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% Cl] = 1.08 [0.67, 1.72]), and overall survival was 94.1% in each treatment group (HR [95% Cl] = 0.99 [0.65, 1.52]).

During the placebo-controlled phase of the major osteoporotic 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% Cl] = 1.75 [0.69, 4.44]). Subject incidence of serious adverse events of malignancy was 1.8% with denosumab and 1.6% with risedronate.

In clinical trials with RGB-14 events related to malignancy were reported with similar or lower frequency than with the reference product.

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

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

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

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

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

Preventability:
No preventive measures are known.

Impact on the risk-benefit balance of the product:
Routine pharmacovigilance activities further characterise the risk of malignancies.

Public health impact:
No significant public health impact is expected.

SVII.3.2. Presentation of the missing information

Not applicable since no missing information has been identified for the product.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

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

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

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires:

Targeted follow-up questionnaires, in line with the reference product, are summarised in a table below.

Table Part III.1: Specific adverse reaction follow-up questionnaires

Targeted follow-up questionnaire	Safety concern	Purpose
Hypocalcaemia	Hypocalcaemia	To monitor the nature of hypocalcaemia
Infection	Skin infection leading to hospitalisation Infection	To monitor the nature of skin infections leading to hospitalisation and infections of any type
Osteonecrosis of the jaw	Osteonecrosis of the jaw	To monitor the nature of ONJ
Hypersensitivity	Hypersensitivity reactions	To monitor the nature of hypersensitivity
Atypical fractures	Atypical femoral fracture	To monitor the nature of AFF
Fracture healing	Fracture healing complications	To monitor the nature of fracture healing complications
Malignancy	Malignancy	To monitor the nature of malignancy

Other forms of routine pharmacovigilance activities:

None.

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance studies/activities are planned.

III.3 Summary Table of additional Pharmacovigilance activities

No additional pharmacovigilance studies/activities are planned.

Part IV: Plans for post-authorisation efficacy studies

No post-authorisation efficacy studies are planned.

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

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

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

Safety concern	Routine risk minimisation activities
Important identified risk	
Hypocalcaemia	Routine risk communication: *SmPC section 4.2, 4.3, 4.4 and 4.8* *PL section 2 and 4* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Recommendation regarding correction and monitoring of calcium levels is provided in SmPC section 4.4* Other risk minimisation measures beyond the Product Information: Legal status: *medical prescription*
Skin infection leading to hospitalisation	Routine risk communication: *SmPC sections 4.4 and 4.8* *PL sections 2 and 4* Other risk minimisation measures beyond the Product Information: Legal status: *medical prescription*
Osteonecrosis of the jaw	Routine risk communication: *SmPC section 4.4 and 4.8* *PL sections 2 and 4* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Oral hygiene and dental management guidance is provided in SmPC section 4.4* Other risk minimisation measures beyond the Product Information: Legal status: *medical prescription*
Hypersensitivity reactions	Routine risk communication: *SmPC sections 4.3 and 4.8* *PL sections 2 and 4* Other risk minimisation measures beyond the Product Information: Legal status: *medical prescription*
Atypical femoral fracture	Routine risk communication: *SmPC section 4.4 and 4.8* *PL sections 2 and 4* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Recommendation for reporting potential symptoms is provided in SmPC section 4.4* Other risk minimisation measures beyond the Product Information: Legal status: *medical prescription*

Safety concern	Routine risk minimisation activities
Hypercalcaemia in paediatric patients receiving denosumab and after treatment discontinuation	Routine risk communication: *SmPC sections 4.2, 4.4 and 4.8* *PL sections 2* Other risk minimisation measures beyond the Product Information: Legal status: *medical prescription*
Important potential risk	
Fracture healing complications	Routine risk communication: *SmPC section 5.3* Other risk minimisation measures beyond the Product Information: Legal status: *medical prescription*
Infection	Routine risk communication: *SmPC section 4.8* *PL section 4* Other risk minimisation measures beyond the Product Information: Legal status: *medical prescription*
Cardiovascular events	Other risk minimisation measures beyond the Product Information: Legal status: *medical prescription*
Malignancy	Other risk minimisation measures beyond the Product Information: Legal status: *medical prescription*

V.2. Additional Risk Minimisation Measures

Important identified risk of Osteonecrosis of the jaw

Patient card

Objectives:

Patient card will be provided to address the risk of 'Osteonecrosis of the jaw'.

Rationale for the additional risk minimisation activity:

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

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

Target audience and planned distribution path:

The patient card will be distributed to prescribers with instructions to provide it to patients.

The patient card will be distributed by mail and prescribers will be provided with contact details to request additional copies of the card. Some national plans may include making the patient card available on a website. The patient card is also available on the website of Junod. QR code to this website is placed within the Patient information leaflet and on the outer packaging of Junod.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Monitoring and evaluating post-marketing safety data in periodic safety update reports.

V.3 Summary of risk minimisation measures

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

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
Hypocalcaemia	Routine risk minimisation measures *SmPC section 4.4, where recommendation regarding correction and monitoring of calcium levels is provided* *SmPC sections 4.2, 4.3 and 4.8* *PL sections 2 and 4* Legal status: *medical prescription* Additional risk minimisation measures *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *AE follow-up questionnaire for hypocalcaemia* Additional pharmacovigilance activities *None*
Skin infection leading to hospitalisation	Routine risk minimisation measures *SmPC sections 4.4 and 4.8* *PL sections 2 and 4* Legal status: *medical prescription* Additional risk minimisation measures *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *AE follow-up questionnaire for infection* Additional pharmacovigilance activities *None*
Osteonecrosis of the jaw	Routine risk minimisation measures *SmPC section 4.4, where oral hygiene and dental management guidance is provided* *SmPC section 4.8* *PL sections 2 and 4* Legal status: *medical prescription* Additional risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *AE follow-up questionnaire for osteonecrosis of the jaw* Additional pharmacovigilance activities *None*

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Patient card	
Hypersensitivity reactions	Routine risk minimisation measures *SmPC sections 4.3 and 4.8* *PL sections 2 and 4* Legal status: *medical prescription* Additional risk minimisation measures *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *AE follow-up questionnaire for hypersensitivity* Additional pharmacovigilance activities *None*
Atypical femoral fracture	Routine risk minimisation measures *SmPC section 4.4, where recommendation for reporting potential symptoms is provided* *SmPC section 4.8* *PL sections 2 and 4* Legal status: *medical prescription* Additional risk minimisation measures *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *AE follow-up questionnaire for atypical femoral fracture* Additional pharmacovigilance activities *None*
Hypercalcaemia in paediatric patients receiving denosumab and after treatment discontinuation	Routine risk minimisation measures *SmPC section 4.2, 4.4 and 4.8* *PL sections 2* Legal status: *medical prescription* Additional risk minimisation measures *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities *None*
Important potential risks		
Fracture healing complications	Routine risk minimisation measures *SmPC section 5.3* Legal status: *medical prescription* Additional risk minimisation measures *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *AE follow-up questionnaire for fracture healing complications* Additional pharmacovigilance activities *None*
Infection	Routine risk minimisation measures *SmPC section 4.8* *PL section 4* Legal status: *medical prescription*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *AE follow-up questionnaire for infection* Additional pharmacovigilance activities

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures *None*	*None*
Cardiovascular events	Routine risk minimisation measures Legal status: *medical prescription* Additional risk minimisation measures *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities *None*
Malignancy	Routine risk minimisation measures Legal status: *medical prescription* Additional risk minimisation measures *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *AE follow-up questionnaire for malignancy* Additional pharmacovigilance activities *None*

Part VI: Summary of the risk management plan

Summary of risk management plan for Junod (denosumab)

This is a summary of the risk management plan (RMP) for Junod. The RMP details important risks of Junod, how these risks can be minimised, and how more information will be obtained about Junod's risks and uncertainties (missing information).
Junod's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Junod should be used.
This summary of the RMP for Junod 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 Junod's RMP.

I. The medicine and what it is used for

Junod is authorised for the treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures; the treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures; and treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture (see SmPC for the full indication). It contains denosumab as the active substance and it is given by subcutaneous injection.
Further information about the evaluation of Junod's benefits can be found in Junod's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage. [Link to the website]

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

Important risks of Junod, together with measures to minimise such risks and the proposed studies for learning more about Junod's risks, are outlined below.
Measures to minimise the risks identified for medicinal products can be:

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

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

In the case of Junod, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.
In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.
If important information that may affect the safe use of Junod is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

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

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

II.B Summary of important risks

Important identified risk: Hypocalcaemia	
Evidence for linking the risk to the medicine	This risk was identified in the phase III, randomised, double-blind, placebo- or active-controlled studies with the reference product.
Risk factors and risk groups	Risk factors include severe renal impairment and hyperphosphatemia. Other risks factors may include a history of hypoparathyroidism, parathyroid hormone resistance, vitamin D deficiency or resistance, thyroid surgery, parathyroid surgery, malabsorption syndromes, excision of small intestine, severe renal impairment (creatinine clearance < 30 mL/min), dialysis, and some medications (Finkelstein 2001[1]).
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.4, where recommendation regarding correction and monitoring of calcium levels is provided* *SmPC sections 4.2, 4.3 and 4.8* *PL sections 2 and 4* Additional risk minimisation measures *None*

[1] *Finkelstein JS. The parathyroid glands, hypercalcemia, and hypocalcemia. Cecil Essentials of Medicine, 5th ed. 2001; 639-648*

Important identified risk: Skin infection leading to hospitalisation	
Evidence for linking the risk to the medicine	This risk was identified in the phase III, randomised, double-blind, placebo- or active-controlled studies with the reference product.
Risk factors and risk groups	Risk factors for infection in general include increasing age, immunosuppression associated with cancer, diabetes, human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), immunosuppressant drugs (e.g., corticosteroids, arthritis medications, and chemotherapy drugs), substance abuse, and malnutrition. Risk factors for skin infection in older patients include skin wounds, peripheral vascular disease, eczema/dermatitis, and venous stasis disorders.
Risk minimisation measures	Routine risk minimisation measures *SmPC sections 4.4 and 4.8* *PL sections 2 and 4* Additional risk minimisation measures *None*

Important identified risk: Osteonecrosis of the jaw	
Evidence for linking the risk to the medicine	This risk was identified in open-label long-term extensions to phase III, randomised, double-blind, placebo-controlled studies with the reference product.
Risk factors and risk groups	Risk factors include duration of exposure to denosumab, prior bisphosphonate use (particularly for extended periods of time), older age, periodontal disease, dentoalveolar surgery, trauma from poorly fitting dentures, malignancy, chemotherapy, corticosteroids, smoking, systemic or regional infection, immune-compromised state predisposing to increased risk of infection, hypercoagulable state secondary to underlying malignancy, and vascular insufficiency due to thrombosis (Mehrotra 2006[2]).
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.4, where oral hygiene and dental management guidance is provided* *SmPC section 4.8* *PL sections 2 and 4* Additional risk minimisation measures *Patient card*

[2] *Mehrotra B, Ruggiero S. Bisphosphonate complications including osteonecrosis of the jaw. Hematology Am Soc Hematol Educ Program. 2006:356-60, 515. doi: 10.1182/asheducation-2006.1.356.*

Important identified risk: Hypersensitivity reactions	
Evidence for linking the risk to the medicine	This risk was identified in the post-marketing setting with the reference product based on a clinically plausible association between administration of denosumab and hypersensitivity events.
Risk factors and risk groups	Known hypersensitivity to denosumab and any of its excipients.
Risk minimisation measures	Routine risk minimisation measures *SmPC sections 4.3 and 4.8* *PL sections 2 and 4* Additional risk minimisation measures *None*

Important identified risk: Atypical Femoral Fracture	
Evidence for linking the risk to the medicine	This risk was identified in an open-label long-term extension to a phase III, randomised, double-blind, active-controlled study with the reference product.
Risk factors and risk groups	Long-term antiresorptive treatment has been associated with atypical femoral fracture. Corticosteroids have also been reported in the literature to potentially be associated with atypical femoral fracture (Meier 2012[3]; Giusti 2011[4]). Atypical femoral fractures have also been reported in patients with certain comorbid conditions (e.g., vitamin D deficiency, rheumatoid arthritis, hypophosphatasia) and with use of bisphosphonates, glucocorticoids, and proton pump inhibitors (Shane 2010[5]).
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.4, where recommendation for reporting potential symptoms is provided* *SmPC section 4.8* *PL sections 2 and 4* Additional risk minimisation measures *None*

[3] Meier RP, Perneger TV, Stern R, Rizzoli R, Peter RE. Increasing occurrence of atypical femoral fractures associated with bisphosphonate use. Arch Intern Med. 2012 Jun 25;172(12):930-6. doi: 10.1001/archinternmed.2012.1796.

[4] Giusti A, Hamdy NA, Dekkers OM, Ramautar SR, Dijkstra S, Papapoulos SE. Atypical fractures and bisphosphonate therapy: a cohort study of patients with femoral fracture with radiographic adjudication of fracture site and features. Bone. 2011 May 1;48(5):966-71. doi: 10.1016/j.bone.2010.12.033.

[5] Shane E, Burr D, Ebeling PR, Abrahamsen B, Adler RA, Brown TD. et al. Whyte M; American Society for Bone and Mineral Research. Atypical subtrochanteric and diaphyseal femoral fractures: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res. 2010 Nov;25(11):2267-94. doi: 10.1002/jbmr.253.

Important identified risk: Hypercalcaemia in paediatric patients receiving denosumab and after treatment discontinuation	
Evidence for linking the risk to the medicine	This risk was identified in clinical trials and from post-marketing setting with the reference product.
Risk factors and risk groups	Paediatric patients with growing skeletons and high bone turnover disease states (such as osteogenesis Imperfecta).
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.2, 4.4 and 4.8* *PL sections 2* Additional risk minimisation measures *None*

Important potential risk: Fracture healing complications	
Evidence for linking the risk to the medicine	This is a theoretical risk based on the potential mechanism of action.
Risk factors and risk groups	General risk factors for fracture healing complications are thought to include older age, diabetes, use of medications such as non-steroidal anti-inflammatory drugs and corticosteroids, smoking, excessive alcohol use, and poor nutrition (Hernandez[6]; Gaston 2007[7]).
Risk minimisation measures	Routine risk minimisation measures *SmPC section 5.3* Additional risk minimisation measures *None*

Important potential risk: Infection	
Evidence for linking the risk to the medicine	This is considered a potential risk based on theoretical concerns which has not been substantiated in the extensive clinical development programme or in the post-marketing setting with the reference product.
Risk factors and risk groups	Risk factors for infection in general include increasing age, immunosuppression associated with cancer, diabetes, HIV/AIDS, immunosuppressant drugs (e.g., corticosteroids, arthritis medications, and chemotherapy drugs), substance abuse, and malnutrition.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.8* *PL section 4* Additional risk minimisation measures *None*

[6] *Hernandez RK, Do TP, Critchlow CW, Dent RE, Jick SS. Patient-related risk factors for fracture-healing complications in the United Kingdom General Practice Research Database. Acta Orthop. 2012 Dec;83(6):653-60. doi: 10.3109/17453674.2012.747054.*

[7] *Gaston MS, Simpson AH. Inhibition of fracture healing. J Bone Joint Surg Br. 2007 Dec;89(12):1553-60. doi: 10.1302/0301-620X.89B12.19671*

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 programme comprises studies of older subject populations (e.g., osteoporosis, cancer) that are likely to have a higher incidence of pre-existing cardiovascular conditions and, thus, a higher incidence of cardiovascular toxicities than that of the general population (Schulz 2004[8] ; Hak 2000[9]). 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 2007[10]; Smith 2004[11]).
Risk minimisation measures	No risk minimisation measures

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 development programme or in the post-marketing setting with the reference product.
Risk factors and risk groups	General factors for risk of malignancy include advancing age, diet, cigarette smoking, excessive ethanol consumption, and numerous environmental toxins. In addition, cancer populations are at increased risk for a second primary malignancy because of their existing malignancy, possible genetic predisposition, and exposure to chemotherapy and radiation treatment (Anand 2008[12] ; WHO Global Status Report on Noncommunicable Diseases 2010[13]).
Risk minimisation measures	No risk minimisation measures

[8] Schulz E, Arfai K, Liu X, Sayre J, Gilsanz V. Aortic calcification and the risk of osteoporosis and fractures. J Clin Endocrinol Metab. 2004 Sep;89(9):4246-53. doi: 10.1210/jc.2003-030964.

[9] Hak AE, Pols HA, van Hemert AM, Hofman A, Witteman JC. Progression of aortic calcification is associated with metacarpal bone loss during menopause: a population-based longitudinal study. Arterioscler Thromb Vasc Biol. 2000 Aug;20(8):1926-31. doi: 10.1161/01.atv.20.8.1926.

[10] Murphy CA, Dargie HJ. Drug-induced cardiovascular disorders. Drug Saf. 2007;30(9):783-804. doi: 10.2165/00002018-200730090-00005.

[11] Smith SC Jr, Milani RV, Arnett DK, Crouse JR 3rd, McDermott MM, Ridker PM. et al. American Heart Association. Atherosclerotic Vascular Disease Conference: Writing Group II: risk factors. Circulation. 2004 Jun 1;109(21):2613-6. doi: 10.1161/01.CIR.0000128519.60762.84.

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II.C Post-authorisation development plan

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

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

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

There are no studies required for Junod.

[redacted]

Annex 4 - Specific adverse drug reaction follow-up forms

Table of contents

DENOSUMAB TARGETED FOLLOW-UP FORM

for

Hypocalcaemia

REPORTER DETAILS	
Name: _____	
E-mail: _____	Phone: _____
☐ Medical doctor / ☐ Pharmacist / ☐ Nurse / ☐ Other	

CASE ADMINISTRATIVE INFORMATION	
Date of report: __/__/____ (*dd/mm/yyyy*)	Batch number of suspected product: _____
Event reported term: _____	Date of event onset: __/__/____ *(dd/mm/yyyy)*
Source: ☐ Post-marketing / ☐ Clinical trial, Study No. _____	

PATIENT DETAILS			
Patient initials:	____	Gender:	☐ Male / ☐ Female
Year of birth:	_____	Age at time of event:	____
Height:	____ ☐ cm / ☐ in	Weight:	____ ☐ kg / ☐ lbs
Ethnic origin:	☐ Caucasian / ☐ Asian / ☐ Black / ☐ Other: ____		

DENOSUMAB ADMINISTRATION / INFORMATION	
Indications:	**Denosumab dose:**
☐ Postmenopausal osteoporosis ☐ Bone loss from hormone ablation therapy Please specify diagnosis: _____ ☐ Advanced cancer with bone metastasis Please specify diagnosis: _____ ☐ Other: _____ ☐ Unknown	☐ 60 mg subcutaneously every 6 months ☐ 120 mg subcutaneously every 4 weeks ☐ Other: _____ ☐ Unknown

Denosumab exposure:	
Denosumab first administered:	__/__/____ *(dd/mm/yyyy)*
Last denosumab dose before event:	__/__/____ *(dd/mm/yyyy)*
Doses of denosumab were skipped:	☐ Yes / ☐ No / ☐ Unknown If yes, please specify: _____
Doses of denosumab given after event began:	☐ Yes / ☐ No / ☐ Unknown If yes, date of first dose following start of event: __/__/____ *(dd/mm/yyyy)*

SIGNS AND SYMPTOMS (Check all that apply)			
☐ Numbness (Specify if involving digits and/or peri-oral region: _____)			
☐ Convulsion	☐ Muscle twitching	☐ Muscle cramping	☐ Paraesthesia
☐ 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 time of event < 4.0 g/dL?	☐ Yes	☐ No	☐ Unknown
If yes, what were the ionised calcium levels?	☐ Yes	☐ No	☐ Unknown
Serum creatinine at time of event was >2.0 X times ULN?	☐ Yes	☐ No	☐ Unknown
Please provide result:	_____ mmol/dL		
Hypocalcaemia-induced ECG changes (QT prolongation)?	☐ Yes	☐ No	☐ Unknown

TREATMENT

Treated only as an outpatient?	☐ Yes	☐ No	☐ Unknown
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:	☐ Yes	☐ No	☐ Unknown
Overall length of hospital stay:	☐ ≤1 day	☐ 1-7 days	☐ >1 day
Anti-arrhythmic medications?	☐ Yes	☐ No	☐ Unknown
If yes, please provide name of medication:	_____		
Please provide dates of treatment:	__/__/____ *(dd/mm/yyyy)*		
Other treatment?	☐ Yes	☐ No	☐ Unknown
If yes, please specify:	_____		

RISK FACTORS (Check all that apply)

Medical history risk factors: ☐ Yes / ☐ No	If yes, please provide dates and details:
☐ Acute pancreatitis	_____
☐ History of parathyroid disease	_____
☐ History of malignancy	_____
☐ Hyperphosphatemia	_____
☐ Recent surgery	_____
☐ History of chronic renal disease	_____
☐ History of hypoalbuminemia	_____
☐ Hypoproteinaemia	_____
☐ Magnesium deficiencyp	_____
☐ Sepsis	_____
☐ Prior hypocalcaemia event (before denosumab treatment)	_____

☐ Vitamin D deficiency

If patient has a history of vitamin D deficiency, were the vitamin D levels normal at the time of event? ☐ Yes / ☐ No

Please provide the vitamin D levels at the time of hypocalcaemia event: _____

Medication risk factors:

Antineoplastic agents?

☐ cisplatin ☐ cytosine arabinoside ☐ Other: _____ ☐ None

Antimicrobials?

☐ pentamidine ☐ ketoconazole ☐ Other: _____ ☐ None

Concomitant medications:

Taking vitamin D supplement?	☐ Yes	☐ No	☐ Unknown

If yes, please provide date and dates: _ _ _ _ _			
Taking calcium supplement? If yes, please provide date and dates: _ _ _ _ _	☐ Yes	☐ No	☐ Unknown
Other concomitant medications: _ _ _ _ _			

Hypocalcaemic event resolved? If yes, please provide date: _ _/_ _/_ _ _ _ *(dd/mm/yyyy)*	☐ Yes	☐ No	☐ Unknown

DENOSUMAB TARGETED FOLLOW-UP FORM

for

Infection

REPORTER DETAILS	
Name: _____	
E-mail: _____	Phone: _____
☐ Medical doctor / ☐ Pharmacist / ☐ Nurse / ☐ Other	

CASE ADMINISTRATIVE INFORMATION	
Date of report: __/__/____ (*dd/mm/yyyy*)	Batch number of suspected product: _____
Event reported term: _____	Date of event onset: __/__/____ *(dd/mm/yyyy)*
Source: ☐ Post-marketing / ☐ Clinical trial, Study No. _____	

PATIENT DETAILS			
Patient initials:	____	Gender:	☐ Male / ☐ Female
Year of birth:	_____	Age at time of event:	____
Height:	____ ☐ cm / ☐ in	Weight:	____ ☐ kg / ☐ lbs
Ethnic origin:	☐ Caucasian / ☐ Asian / ☐ Black / ☐ Other: ____		

DENOSUMAB ADMINISTRATION / INFORMATION	
Indications:	**Denosumab dose:**
☐ Post-menopausal osteoporosis ☐ Bone loss from hormone ablation therapy Please specify diagnosis: _____ ☐ Advanced cancer with bone metastasis Please specify diagnosis: _____ ☐ Other: _____ ☐ Unknown	☐ 60 mg subcutaneously every 6 months ☐ 120 mg subcutaneously every 4 weeks ☐ Other: _____ ☐ Unknown

Denosumab exposure:	
Denosumab first administered:	__/__/____ *(dd/mm/yyyy)*
Last denosumab dose before event:	__/__/____ *(dd/mm/yyyy)*
Doses of denosumab were skipped:	☐ Yes / ☐ No / ☐ Unknown If yes, please specify: _____
Doses of denosumab given after event began:	☐ Yes / ☐ No / ☐ Unknown If yes, date of first dose following start of event: __/__/____ *(dd/mm/yyyy)*

SIGNS AND SYMPTOMS (Check all that appliy, provide dates of onset, resolution, if available)

Sign	Date of onset *(dd/mm/yyyy)*	Resolution	Other information
☐ Fever	__/__/____	_____	_____
☐ Cough	__/__/____	_____	_____
☐ Swelling Location _____	__/__/____	_____	_____
☐ Shortness of breath	__/__/____	_____	_____
☐ Pain Location _____	__/__/____	_____	_____
☐ Rash Location _____	__/__/____	_____	_____

☐ Prolonged fatigue	__/__/____	_____	_____
☐ Diarrhoea	__/__/____	_____	_____
☐ Discharge Location _____ Description: _____	__/__/____	_____	_____
☐ Chills	__/__/____	_____	_____
☐ Nights sweats	__/__/____	_____	_____
☐ Other: _____	__/__/____	_____	_____

Organ system affected:

☐ Cardiac
☐ Ear/nose
☐ Throat
☐ Respiratory
☐ Gastrointestinal
☐ Kidney/genito-urinary
☐ Musculoskeletal (incl. joints)
☐ Systemic (bacteraemia and/or sepsis
☐ Nervous (cerebrospinal fluid)
☐ Other: _____
☐ Skin, location: _____

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

Diagnostic	Results/ Units	Reference Range/ Units	Date *(dd/mm/yyyy)*	Attachment
_____	_____	_____	__/__/____	☐
_____	_____	_____	__/__/____	☐
_____	_____	_____	__/__/____	☐
_____	_____	_____	__/__/____	☐
_____	_____	_____	__/__/____	☐
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_____	_____	_____	__/__/____	☐
_____	_____	_____	__/__/____	☐
_____	_____	_____	__/__/____	☐

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

CHECK WHICH INFECTION APPLIES

- ☐ Cardiac infections:
  - ☐ Endocarditis: _____
  - ☐ Pericarditis (purulent; tuberculous): _____
  - ☐ Other, please specify: _____
- ☐ Ear and labyrinth infections:
  - ☐ Otitis media: _____
  - ☐ Otitis externa: _____
  - ☐ Other, please specify: _____
- ☐ Gastrointestinal/abdominal infections:
  - ☐ Colitis: _____
  - ☐ Diverticulitis: _____
  - ☐ Appendicitis: _____
  - ☐ Abdominal sepsis (incl. 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: _____
  - ☐ Legionella pneumonia: _____
  - ☐ Mycoplasma pneumonia: _____
  - ☐ Other, please specify: _____
- ☐ Kidney and genito-urinary tract infections:
  - ☐ Cystitis: _____
  - ☐ Pyelonephritis: _____
  - ☐ Urinary tract infection: _____
  - ☐ Other, please specify: _____
- ☐ Systemic infections:
  - ☐ Bacteraemia: _____
  - ☐ Sepsis: _____
  - ☐ Toxic shock syndrome: _____
  - ☐ Other, please specify: _____
- ☐ Wound and skin infections:
  - ☐ Cellulitis: _____
  - ☐ Erysipelas: _____
  - ☐ Necrotizing fasciitis: _____
  - ☐ Abscess: _____
  - ☐ Other, please specify: _____
  - ☐ Opportunistic infections:
  - ☐ Aspergillus (invasive forms only): _____
  - ☐ Blastomycosis pulmonary or extra-pulmonary infections: _____
  - ☐ Candidiasis systemic: _____
  - ☐ Coccidioidomycosis 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 lung, 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:_____
- ☐ Other infections, please specify: _____
- ☐ Parasitic evaluation (ova, etc.): _____

DIAGNOSTICS

☐ Culture done: ☐ Yes / ☐ No / ☐ Unknown

If yes, check which apply:

☐ Blood culture — Culture positive? ☐ Yes / ☐ No / ☐ Unknown
If yes, which Pathogen identified: _____ ☐ Bacterial / ☐ Fungal / ☐ Viral

☐ Urine culture	Culture positive? If yes, which Pathogen identified:	☐ Yes / ☐ No / ☐ Unknown ☐ Bacterial / ☐ Fungal / ☐ Viral _____
☐ Sputum culture	Culture positive? If yes, which Pathogen identified:	☐ Yes / ☐ No / ☐ Unknown ☐ Bacterial / ☐ Fungal / ☐ Viral _____
☐ Synovial culture	Culture positive? If yes, which Pathogen identified:	☐ Yes / ☐ No / ☐ Unknown ☐ Bacterial / ☐ Fungal / ☐ Viral _____
☐ Cerebrospinal fluid culture	Culture positive? If yes, which Pathogen identified:	☐ Yes / ☐ No / ☐ Unknown ☐ Bacterial / ☐ Fungal / ☐ Viral _____
☐ Tissue culture	Culture positive? If yes, which Pathogen identified:	☐ Yes / ☐ No / ☐ Unknown ☐ Bacterial / ☐ Fungal / ☐ Viral _____
☐ Catheter Tip/Line	Culture positive? If yes, which Pathogen identified:	☐ Yes / ☐ No / ☐ Unknown ☐ Bacterial / ☐ Fungal / ☐ Viral _____
☐ PPD placement	If yes, PPD positive	☐ Yes / ☐ No / ☐ Unknown ☐ Yes / ☐ No / ☐ Unknown
☐ Parasitic evaluation (ova, etc.)	☐ Yes / ☐ No / ☐ Unknown	
☐ X-ray	☐ Yes / ☐ No / ☐ Unknown	
☐ MRI	☐ Yes / ☐ No / ☐ Unknown	
☐ CT scan	☐ Yes / ☐ No / ☐ Unknown	
☐ Bone scan	☐ Yes / ☐ No / ☐ 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	☐ Yes / ☐ No / ☐ Unknown If yes, route: ☐ IV / ☐ Oral / ☐ Both oral and IV / ☐ SC
☐ Required hospital admission	☐ Yes / ☐ No / ☐ Unknown
☐ ICU admission	☐ Yes / ☐ No / ☐ Unknown If yes, reason for ICU admission: _____
☐ Overall length of hospital stay	☐ <1 day / ☐ >1 day or <7 days / ☐ >7 days
☐ In-hospital antibiotics	☐ Yes / ☐ No / ☐ Unknown If yes, route: ☐ IV / ☐ Oral / ☐ Both oral and IV / ☐ SC
☐ Other in-hospital treatment:	
☐ Antivirals	☐ Yes / ☐ No / ☐ Unknown If yes, route: ☐ IV / ☐ Oral
☐ Antifungals	☐ Yes / ☐ No / ☐ Unknown If yes, route: ☐ IV / ☐ Oral
☐ Surgery	☐ Yes / ☐ No / ☐ Unknown
☐ Hyperbaric oxygen	☐ Yes / ☐ No / ☐ 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: _____
- ☐ Steroid exposure: _____
- ☐ Insect / tich bite: _____
- ☐ Drug or IV drug abuse (specify type, amount, frequency): _____
- ☐ Alcohol / tobacco use (specify type, amount, frequency): _____
- ☐ Indwelling catheters: _____
- ☐ Exposure to infections agents: _____
  - ☐ Personal contact
  - ☐ Body fluids
  - ☐ Share personal items (razor, needles, etc.)
  - ☐ Potentially contaminated food / liquid
  - ☐ Hospital acquired
  - ☐ Other: _____
- ☐ Recent skin injury: _____
- ☐ Recent travel: _____
- ☐ Exposure to animals / zoonotic diseases (exposure to infected animal): _____
- ☐ Unprotected sex: _____
- ☐ Immobility: _____
- ☐ Nursing home resident: _____
- ☐ Occupational exposure: _____
- ☐ Ostomy: _____
- ☐ Post influenza: _____
- ☐ Surgery <30 days: _____
- ☐ TB exposure: _____
- ☐ Other history / risk factors: _____

DENOSUMAB TARGETED FOLLOW-UP FORM

for

Osteonecrosis of the jaw

REPORTER DETAILS	
Name: _____	
E-mail: _____	Phone: _____
☐ Medical doctor / ☐ Pharmacist / ☐ Nurse / ☐ Other	

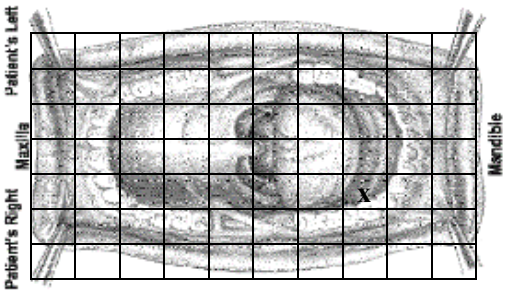
CASE ADMINISTRATIVE INFORMATION	
Date of report: __/__/____ (*dd/mm/yyyy*)	Batch number of suspected product: _____
Event reported term: _____	Date of event onset: __/__/____ *(dd/mm/yyyy)*
Source: ☐ Post-marketing / ☐ Clinical trial, Study No. _____	

PATIENT DETAILS			
Patient initials:	____	Gender:	☐ Male / ☐ Female
Year of birth:	_____	Age at time of event:	____
Height:	____ ☐ cm / ☐ in	Weight:	____ ☐ kg / ☐ lbs
Ethnic origin:	☐ Caucasian / ☐ Asian / ☐ Black / ☐ Other: ____		

DENOSUMAB ADMINISTRATION / INFORMATION	
Indications:	**Denosumab dose:**
☐ Post-menopausal osteoporosis ☐ Bone loss from hormone ablation therapy Please specify diagnosis: _____ ☐ Advanced cancer with bone metastasis Please specify diagnosis: _____ ☐ Other: _____ ☐ Unknown	☐ 60 mg subcutaneously every 6 months ☐ 120 mg subcutaneously every 4 weeks ☐ Other: _____ ☐ Unknown

Denosumab exposure:	
Denosumab first administered:	__/__/____ *(dd/mm/yyyy)*
Last denosumab dose before event:	__/__/____ *(dd/mm/yyyy)*
Doses of denosumab were skipped:	☐ Yes / ☐ No / ☐ Unknown If yes, please specify: _____
Doses of denosumab given after event began:	☐ Yes / ☐ No / ☐ Unknown If yes, date of first dose following start of event: __/__/____ *(dd/mm/yyyy)*

EVIDENCE OF EXPOSED BONE
Visible evidence of exposed bone, or bone that can be probed through an intraoral or extraoral fistula(e) in the maxillofacial region: ☐ Yes ☐ No ☐ Unknown Please describe: _____
Date exposed bone was first visualised/probed: __/__/____ *(dd/mm/yyyy)*
Exposed bone or probed bone that has persisted for more than eight weeks: ☐ Yes ☐ No ☐ Unknown Please describe: _____
Prior history of radiation therapy to jaw: ☐ Yes ☐ No ☐ Unknown Please describe: _____
Prior history of metastatic disease to jaw: ☐ Yes ☐ No ☐ Unknown Please describe: _____

Please describe location(s):	Please indicate the location of involved area(s) on the picture below (mark site(s) clearly with 'X').
☐ 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, please specify	

ORAL FINDINGS		
Evidence of infection: Please describe: _____	☐ Yes ☐ No ☐ Unknown	
Exposed bone at the site of extraction:	☐ Yes ☐ No ☐ Unknown	
Complete coverage of involved area(s) by mucosa:	☐ Yes ☐ No	Date of complete mucosal coverage: __/__/____ *(dd/mm/yyyy)* ☐ Unknown

CLINICAL SYMPTOMS
Date of first clinical signs/symptoms in the mouth (e.g., infection, pain, inflammation): __/__/____ *(dd/mm/yyyy)* Please describe the clinical signs/symptoms/location: _____

CONSULTATIONS		
Dental/oral surgery/ stomatology consultations:	☐ Yes ☐ No	Date of examination: __/__/____ *(dd/mm/yyyy)* ☐ Unknown
Please provide any consult reports, radiographs, pictures, if available		

TREATMENT INFORMATION (Please indicate what treatments were administered)	
Antibiotics:	☐ Yes ☐ No ☐ Unknown If yes, agent(s)/route/dose: _____ Start date: __/__/____ *(dd/mm/yyyy)* Stop date: __/__/____ *(dd/mm/yyyy)* Please describe outcomes of treatment: _____
Oral rinses:	☐ Yes ☐ No ☐ Unknown If yes, agent(s)/dose: _____ Please describe outcomes of treatment: _____
Oral surgery:	☐ Yes ☐ No ☐ Unknown If yes, type of surgery: _____ Start date: __/__/____ *(dd/mm/yyyy)* Stop date: __/__/____ *(dd/mm/yyyy)* Please describe outcomes of treatment: _____
Hospitalisation:	☐ Yes ☐ No ☐ Unknown If yes, reason for hospitalisation: _____ Start date: __/__/____ *(dd/mm/yyyy)* End date: __/__/____ *(dd/mm/yyyy)* Please describe outcomes of treatment: _____

DENTAL HISTORY	
History of poor oral hygiene:	☐ Yes ☐ No ☐ Unknown
Dental extraction recently:	☐ Yes ☐ No ☐ Unknown If yes, date of procedure: __/__/____ *(dd/mm/yyyy)*

Dental surgery recently:	☐ Yes ☐ No ☐ Unknown If yes, date of procedure: __/__/____ *(dd/mm/yyyy)*
Periodontal disease incl. gingival bleeding, calculus, etc.:	☐ Yes ☐ No ☐ Unknown Start date: __/__/____ *(dd/mm/yyyy)* Stop date: __/__/____ *(dd/mm/yyyy)*
Draining fistula in affected area:	☐ Yes ☐ No ☐ Unknown Start date: __/__/____ *(dd/mm/yyyy)* Stop date: __/__/____ *(dd/mm/yyyy)*
Dental abscess in affected area:	☐ Yes ☐ No ☐ Unknown Start date: __/__/____ *(dd/mm/yyyy)* Stop date: __/__/____ *(dd/mm/yyyy)*
Osteomyelitis in affected area:	☐ Yes ☐ No ☐ Unknown Start date: __/__/____ *(dd/mm/yyyy)* Stop date: __/__/____ *(dd/mm/yyyy)*
Root-canal treatment near affected area:	☐ Yes ☐ No ☐ Unknown If yes, date of procedure: __/__/____ *(dd/mm/yyyy)*
Dental treatment, surgery or tooth extraction to the involved area within the last 4-6 months prior to the onset of the oral lesion	☐ Yes ☐ No ☐ Unknown
History of dentures/dental appliance/implant:	☐ Yes ☐ No ☐ Unknown If yes, please specify: ☐ Upper ☐ Lower
Area of lesion at or near a contact point:	☐ Yes ☐ No ☐ Unknown

MEDICATIONS	
Bisphosphonate (per os):	☐ Yes ☐ No ☐ Unknown If yes, agent(s)/route/dose: _____ Start date: __/__/____ *(dd/mm/yyyy)* Stop date: __/__/____ *(dd/mm/yyyy)*
Bisphosphonate (intravenously):	☐ Yes ☐ No ☐ Unknown If yes, agent(s)/route/dose: _____ Start date: __/__/____ *(dd/mm/yyyy)* Stop date: __/__/____ *(dd/mm/yyyy)*
Glucocorticoid use within the past 12 months:	☐ Yes ☐ No ☐ Unknown If yes, agent(s)/route/dose: _____ Start date: __/__/____ *(dd/mm/yyyy)* Stop date: __/__/____ *(dd/mm/yyyy)*
Immunosuppressant use within the past 12 months:	☐ Yes ☐ No ☐ Unknown If yes, agent(s)/route/dose: _____ Start date: __/__/____ *(dd/mm/yyyy)* Stop date: __/__/____ *(dd/mm/yyyy)*
Chemotherapy within the past 12 months:	☐ Yes ☐ No ☐ Unknown If yes, agent(s)/route/dose: _____ Start date: __/__/____ *(dd/mm/yyyy)* Stop date: __/__/____ *(dd/mm/yyyy)*
Anti-angiogenic agents (e.g., bevacizumab) within the past 12 months:	☐ Yes ☐ No ☐ Unknown If yes, agent(s)/route/dose: _____ Start date: __/__/____ *(dd/mm/yyyy)* Stop date: __/__/____ *(dd/mm/yyyy)*

OTHER HISTORY	
Current smoker:	☐ Yes ☐ No ☐ Unknown If yes, estimated number of pack-years: _____ If past smoker, stop date: __/__/____ *(dd/mm/yyyy)*
Alcohol	☐ Yes ☐ No ☐ Unknown

consumption:	If yes, estimated drinks per week: _____
Diabetes:	☐ Yes ☐ No ☐ Unknown If yes: ☐ Type I ☐ Type II

DENOSUMAB TARGETED FOLLOW-UP FORM

for

Hypersensitivity

REPORTER DETAILS	
Name: _____	
E-mail: _____	Phone: _____
☐ Medical doctor / ☐ Pharmacist / ☐ Nurse / ☐ Other	

CASE ADMINISTRATIVE INFORMATION	
Date of report: __/__/____ (*dd/mm/yyyy*)	Batch number of suspected product: _____
Event reported term: _____	Date of event onset: __/__/____ *(dd/mm/yyyy)*
Source: ☐ Post-marketing / ☐ Clinical trial, Study No. _____	

PATIENT DETAILS			
Patient initials:	____	Gender:	☐ Male / ☐ Female
Year of birth:	_____	Age at time of event:	____
Height:	____ ☐ cm / ☐ in	Weight:	____ ☐ kg / ☐ lbs
Ethnic origin:	☐ Caucasian / ☐ Asian / ☐ Black / ☐ Other: ____		

DENOSUMAB ADMINISTRATION / INFORMATION	
Indications:	**Denosumab dose:**
☐ Postmenopausal osteoporosis ☐ Bone loss from hormone ablation therapy Please specify diagnosis: _____ ☐ Advanced cancer with bone metastasis Please specify diagnosis: _____ ☐ Other: _____ ☐ Unknown	☐ 60 mg subcutaneously every 6 months ☐ 120 mg subcutaneously every 4 weeks ☐ Other: _____ ☐ Unknown

Denosumab exposure:	
Denosumab first administered:	__/__/____ *(dd/mm/yyyy)*
Last denosumab dose before event:	__/__/____ *(dd/mm/yyyy)*
Doses of denosumab were skipped:	☐ Yes / ☐ No / ☐ Unknown If yes, please specify: _____
Doses of denosumab given after event began:	☐ Yes / ☐ No / ☐ Unknown If yes, date of first dose following start of event: __/__/____ *(dd/mm/yyyy)*

SIGNS AND SYMPTOMS			
☐ Anaphylaxis	☐ Hypotension	☐ Stridor	☐ Angioneurotic oedema
☐ Urticaria	☐ Wheezing	☐ Diarrhoea	☐ Laryngeal oedema
☐ Colic	☐ Rash	☐ Pruritis	☐ Shortness of breath
☐ Facial oedema	☐ Tachycardia	☐ Swelling	☐ Other, specify: _____

EVALUATIONS, DIGANOSIS AND LABORATORY MEASURES (Please indicate and attach copy of report if available)								
	Results at BASELINE (prior to denosumab)				**Results at TIME OF EVENT**			
Diagnostic	**Results/Units**	**Reference range/Units**	**Date *(dd/mm/yyyy)***	**Report attached**	**Results/Units**	**Reference range/Units**	**Date *(dd/mm/yyyy)***	**Report attached**
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^{2+}	_____	_____	__/__/____	☐	_____	_____	__/__/____	☐
Cl^-	_____	_____	__/__/____	☐	_____	_____	__/__/____	☐
CrCl	_____	_____	__/__/____	☐	_____	_____	__/__/____	☐

TREATMENT	
☐ ER corticosteroids	☐ Yes / ☐ No / ☐ Unknown If yes, route: ☐ IV / ☐ Oral / ☐ Both oral and IV
☐ ER antihistaminics	☐ Yes / ☐ No / ☐ Unknown If yes, route: ☐ IV / ☐ Oral / ☐ Both oral and IV
☐ Required hospital admission ☐ Overall length of hospital stay	☐ Yes / ☐ No / ☐ Unknown ☐ <1 day / ☐ >1 day or <7 days / ☐ >7 days
☐ ICU admission ☐ Overall length of hospital stay	☐ Yes / ☐ No / ☐ Unknown ☐ <1 day / ☐ >1 day or <7 days / ☐ >7 days
☐ Other in-hospital treatment:	
☐ Corticosteroids	☐ Yes / ☐ No / ☐ Unknown If yes, route: ☐ IV / ☐ Oral / ☐ Both oral and IV
☐ Antihistaminics	☐ Yes / ☐ No / ☐ Unknown If yes, route: ☐ IV / ☐ Oral / ☐ Both oral and IV
☐ 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	☐ Rifampin
☐ Dapsone	☐ Antibiotics:
☐ Penicillamine	☐ Beta-lactams including penicillin and cephalosporin
☐ Anticonvulsants:	☐ Macrolides
☐ Phenytoin	☐ Sulfonamides
☐ Carbamazepine	☐ Quinolones
☐ Phenobarbital	

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*): _ _ _ _ _	

DENOSUMAB TARGETED FOLLOW-UP FORM
for
Atypical fractures
(low energy, subtrochanteric / femoral shaft fractures)

REPORTER DETAILS	
Name: _____	
E-mail: _____	Phone: _____
☐ Medical doctor / ☐ Pharmacist / ☐ Nurse / ☐ Other	

CASE ADMINISTRATIVE INFORMATION	
Date of report: __/__/____ (*dd/mm/yyyy*)	Batch number of suspected product: _____
Event reported term: _____	Date of event onset: __/__/____ *(dd/mm/yyyy)*
Source: ☐ Post-marketing / ☐ Clinical trial, Study No. _____	

PATIENT DETAILS			
Patient initials:	____	Gender:	☐ Male / ☐ Female
Year of birth:	_____	Age at time of event:	____
Height:	____ ☐ cm / ☐ in	Weight:	____ ☐ kg / ☐ lbs
Ethnic origin:	☐ Caucasian / ☐ Asian / ☐ Black / ☐ Other: ____		

DENOSUMAB ADMINISTRATION / INFORMATION	
Indications:	**Denosumab dose:**
☐ Post-menopausal osteoporosis ☐ Bone loss from hormone ablation therapy Please specify diagnosis: _____ ☐ Advanced cancer with bone metastasis Please specify diagnosis: _____ ☐ Other: _____ ☐ Unknown	☐ 60 mg subcutaneously every 6 months ☐ 120 mg subcutaneously every 4 weeks ☐ Other: _____ ☐ Unknown

Denosumab exposure:	
Denosumab first administered:	__/__/____ *(dd/mm/yyyy)*
Last denosumab dose before event:	__/__/____ *(dd/mm/yyyy)*
Doses of denosumab were skipped:	☐ Yes / ☐ No / ☐ Unknown If yes, please specify: _____
Doses of denosumab given after event began:	☐ Yes / ☐ No / ☐ Unknown If yes, date of first dose following start of event: __/__/____ *(dd/mm/yyyy)*

DIAGNOSIS	
Location of fracture: ☐ Femur neck ☐ Femur distal ☐ Femur midshaft ☐ Femur intertrochanter ☐ Femur subtrochanter ☐ Other location, please specify _____	**Type of trauma reported at time of fracture:** ☐ No trauma ☐ Fall from standing height or less ☐ Fall on stairs, steps or curbs ☐ Fall from the height of stool, chair, first rung on a ladder or equivalent (about 20 inches / 51 cm) ☐ Minimal trauma other than a fall
Diagnostic imaging used to confirm fracture: ☐ X-ray / ☐ CT scan / ☐ MRI Date of imaging at time of femur fracture:	

_ _/_ _/_ _ _ _ *(dd/mm/yyyy)* ☐ **Please attach a copy of applicable radiology report(s).**	☐ Fall from higher than the height of a stool, chair, first rung on a ladder or equivalent (>20 inches / 51 cm) ☐ Severe trauma other than a fall (e.g., car accident) ☐ Unknown type of trauma
Was this a pathological fracture associated with bone tumour or miscellaneous bone diseases (e.g., Paget's disease, fibrous dysplasia)? ☐ Yes / ☐ No / ☐ Unknown	**Early symptom of pain over fracture site:** ☐ Pain at site at rest ☐ Pain at site with weight bearing ☐ None
Type of fracture: ☐ Transverse ☐ Oblique ☐ Spiral ☐ Not reported	**Fracture healed (union) within 6 months?** ☐ Yes / ☐ No / ☐ Unknown If yes: Date of fracture union: _ _/_ _/_ _ _ _ *(dd/mm/yyyy)* Patient able to walk without assistance: ☐ Yes / ☐ No / ☐ Unknown Fracture union confirmed through imaging: ☐ Yes / ☐ No / ☐ Unknown If yes, check all diagnostic imaging that applies: ☐ X-ray / ☐ CT scan / ☐ MRI
Fracture radiology report includes: Simple transverse or oblique (30°) fracture with breaking of the cortex: ☐ Yes / ☐ No / ☐ Not reported Diffuse cortical thickening of the proximal femoral shaft: ☐ Yes / ☐ No / ☐ Not reported	

TREATMENT (Please provide dates and indicate attachments if available)

Methods to reduce and set fracture:	Date *(dd/mm/yyyy)*	Attachment
☐ Non-surgical reduction	_ _/_ _/_ _ _ _	☐
☐ Casting	_ _/_ _/_ _ _ _	☐
☐ Surgery	_ _/_ _/_ _ _ _	☐
☐ Revision surgery (2nd surgery)	_ _/_ _/_ _ _ _	☐
☐ Other: _ _ _ _ _		
☐ Unknown: _ _ _ _ _		

MEDICAL HISTORY (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	**Prior osteoporosis therapy:** ☐ Oestrogen ☐ Selective oestrogen receptor modulator ☐ Bisphosphonate: ☐ Intravenous ☐ Oral If yes, how long has the therapy been received? _ _ _ _ _ (months, years) ☐ Parathyroid hormone
Cancer: Evidence of any metastases: ☐ Yes / ☐ No / ☐ Unknown If yes, did metastasis involve bone? ☐ Yes / ☐ No / ☐ Unknown Metastasis in femur where fracture occurred? ☐ Yes / ☐ No / ☐ Unknown	
Past medical and surgical history: _ _ _ _ _	
Medication history (include dose, frequency, and dates of treatment): _ _ _ _ _	
Copies of records/consults/radiology report attached? ☐ Yes / ☐ No	

DENOSUMAB TARGETED FOLLOW-UP FORM

for

Fracture healing

REPORTER DETAILS	
Name: _____	
E-mail: _____	Phone: _____
☐ Medical doctor / ☐ Pharmacist / ☐ Nurse / ☐ Other	

CASE ADMINISTRATIVE INFORMATION	
Date of report: __/__/____ (*dd/mm/yyyy*)	Batch number of suspected product: _____
Event reported term: _____	Date of event onset: __/__/____ *(dd/mm/yyyy)*
Source: ☐ Post-marketing / ☐ Clinical trial, Study No. _____	

PATIENT DETAILS			
Patient initials:	____	Gender:	☐ Male / ☐ Female
Year of birth:	_____	Age at time of event:	____
Height:	____ ☐ cm / ☐ in	Weight:	____ ☐ kg / ☐ lbs
Ethnic origin:	☐ Caucasian / ☐ Asian / ☐ Black / ☐ Other: ____		

DENOSUMAB ADMINISTRATION / INFORMATION	
Indications:	**Denosumab dose:**
☐ Post-menopausal osteoporosis ☐ Bone loss from hormone ablation therapy Please specify diagnosis: _____ ☐ Advanced cancer with bone metastasis Please specify diagnosis: _____ ☐ Other: _____ ☐ Unknown	☐ 60 mg subcutaneously every 6 months ☐ 120 mg subcutaneously every 4 weeks ☐ Other: _____ ☐ Unknown

Denosumab exposure:	
Denosumab first administered:	__/__/____ *(dd/mm/yyyy)*
Last denosumab dose before event:	__/__/____ *(dd/mm/yyyy)*
Doses of denosumab were skipped:	☐ Yes / ☐ No / ☐ Unknown If yes, please specify: _____
Doses of denosumab given after event began:	☐ Yes / ☐ No / ☐ Unknown If yes, date of first dose following start of event: __/__/____ *(dd/mm/yyyy)*

DIAGNOSIS	
Date of fracture:	__/__/____ *(dd/mm/yyyy)*
Date of fracture delayed healing:	__/__/____ *(dd/mm/yyyy)*
Date of fracture non-healing:	__/__/____ *(dd/mm/yyyy)*

Location of fracture:	
☐ Upper body (i.e., above waist) Specify location (check all that apply): ☐ Cervical spine ☐ Radius ☐ Clavicle ☐ Rib ☐ Wrist/carpal ☐ Scapula ☐ Head/face/skull ☐ Shoulder	☐ Lower body (i.e., below waist) Specify location (check all that apply): ☐ Ankle ☐ Hip ☐ Patella ☐ Pelvis ☐ Tibia ☐ Fibula ☐ Foot /tarsal /metatarsal /phalange

☐ Humerus ☐ Sternum ☐ Olecranon ☐ Ulna ☐ Hand/metacarpal/phalange ☐ Other: _____	☐ Femur (specify location: neck, subtrochanteric, mid shaft, etc.): _____ ☐ 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	☐ Poor immobilization of segments
☐ Soft tissue injury	☐ Unknown	☐ Poor alignment
☐ Pathologic		

TREATMENT (Please provide dates and indicate attachments if available)

Methods to reduce and set fracture:	Date *(dd/mm/yyyy)*	Attachment
☐ Non-surgical reduction	__/__/____	☐
☐ Casting	__/__/____	☐
☐ Surgery	__/__/____	☐
☐ Revision surgery (2nd surgery)	__/__/____	☐
☐ Traction	__/__/____	☐
☐ Other: _____		
☐ Unknown: _____		

Did the fracture heal (union)?	☐ Yes / ☐ No / ☐ Unknown
If yes, provide date of union:	__/__/____ *(dd/mm/yyyy)*
If yes, was the healing confirmed through imaging?	☐ Yes / ☐ No / ☐ Unknown
If yes, what diagnostic imaging?	☐ X-ray / ☐ CT scan / ☐ MRI
If yes, is the patient able to walk without assistance?	☐ Yes / ☐ No / ☐ Unknown

MEDICAL HISTORY (Check all that apply, provide dates and attach relevant reports)
- ☐ Current smoker/tobacco user: _____
- ☐ History of current corticosteroid use: _____
- ☐ Prior fracture history:_____.
- ☐ Diabetes: _____

DENOSUMAB TARGETED FOLLOW-UP FORM

for

Malignancy

REPORTER DETAILS	
Name: _____	
E-mail: _____	Phone: _____
☐ Medical doctor / ☐ Pharmacist / ☐ Nurse / ☐ Other	

CASE ADMINISTRATIVE INFORMATION	
Date of report: __/__/____ (*dd/mm/yyyy*)	Batch number of suspected product: _____
Event reported term: _____	Date of event onset: __/__/____ *(dd/mm/yyyy)*
Source: ☐ Post-marketing / ☐ Clinical trial, Study No. _____	

PATIENT DETAILS			
Patient initials:	____	Gender:	☐ Male / ☐ Female
Year of birth:	_____	Age at time of event:	____
Height:	____ ☐ cm / ☐ in	Weight:	____ ☐ kg / ☐ lbs
Ethnic origin:	☐ Caucasian / ☐ Asian / ☐ Black / ☐ Other: ____		

DENOSUMAB ADMINISTRATION / INFORMATION	
Indications:	**Denosumab dose:**
☐ Postmenopausal osteoporosis ☐ Bone loss from hormone ablation therapy Please specify diagnosis: _____ ☐ Advanced cancer with bone metastasis Please specify diagnosis: _____ ☐ Other: _____ ☐ Unknown	☐ 60 mg subcutaneously every 6 months ☐ 120 mg subcutaneously every 4 weeks ☐ Other: _____ ☐ Unknown

Denosumab exposure:	
Denosumab first administered:	__/__/____ *(dd/mm/yyyy)*
Last denosumab dose before event:	__/__/____ *(dd/mm/yyyy)*
Doses of denosumab were skipped:	☐ Yes / ☐ No / ☐ Unknown If yes, please specify: _____
Doses of denosumab given after event began:	☐ Yes / ☐ No / ☐ Unknown If yes, date of first dose following start of event: __/__/____ *(dd/mm/yyyy)*

MALIGNANCY			
Is this a new primary malignancy?	☐ Yes	☐ No	☐ Unknown
If no, is this a recurrence of previous cancer?	☐ Yes	☐ No	☐ Unknown
Does patient have history of other malignancy?	☐ Yes	☐ No	☐ Unknown
If yes, date of prior cancer: __/__/____ *(dd/mm/yyyy)* Tumour stage if known: _____			
Primary site of malignancy: _____			

TUMOUR STAGE			
Tumour Size: ☐ TX / ☐ T0 / ☐ Tis / ☐ T1 / ☐ T2 / ☐ T3 / ☐ T4 Tumour Grade: ☐ GX / ☐ G1 / ☐ G2 / ☐ G3			
Localised (no regional involvement/no distant metastasis)? If yes, skip next 2 questions Lymph Node Involvement: ☐ NX / ☐ N1 / ☐ N2 / ☐ N3 Metastases: ☐ MX / ☐ M0 / ☐ M1		☐ Yes	☐ No

TREATMENT			
Hospitalised?	☐ Yes	☐ No	☐ Unknown
ICU admission?	☐ ≤ 1 day	☐ 1-7 days	☐ > 7 days
Overall length of hospital stay:	☐ Yes	☐ No	☐ Unknown
Surgical treatment?	☐ Yes	☐ No	☐ Unknown
Chemotherapy (includes biologics)?	☐ Yes	☐ No	☐ Unknown
Hormonal treatment?	☐ Yes	☐ No	☐ Unknown
Radiation treatment?	☐ Yes	☐ No	☐ Unknown
Bone marrow transplant? If yes: ☐ autologous / ☐ heterologous	☐ Yes	☐ No	☐ Unknown
Was the malignancy treated with curative intention?	☐ Yes	☐ No	☐ Unknown

RISK FACTORS (Check all that apply)	
☐ Smoking	☐ Positive family history: ☐ Same cancer ☐ Different cancer
☐ Prior Malignancy	
☐ Prior therapeutic radiation exposure	
☐ Environmental exposure, please specify: _____	

[redacted]

Annex 6 - Details of proposed additional risk minimisation activities

Key messages of the additional risk minimisation measures

Patient card

Patient card for Osteonecrosis of the jaw will be distributed to prescribers of Junod with background information on the purpose of the patient card and instructions to provide it to patients.

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

- The risk of osteonecrosis of the jaw during treatment with Junod;
- 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 the treatment;
- The need to inform their dentist of treatment with Junod and to contact their doctor and dentist if problems with the mouth or teeth occur during treatment;
- The need to contact their doctor and dentist immediately if they experience any problems with their mouth or teeth such as loose teeth, pain or swelling, non-healing of sores or discharge.

[redacted]