GEDEON RICHTER PLC.

RISK MANAGEMENT PLAN

FOR

YAXWER 120 mg solution for injection

EU Risk Management Plan for YAXWER (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**
QPPV signature	The electronic signature has been applied at the end of the document
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)	YAXWER
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: YAXWER is a human monoclonal antibody of the immunoglobulin G2 subclass, biosimilar to the licensed denosumab, XGEVA, 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: Prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with advanced malignancies involving bone. Treatment of adults and skeletally mature adolescents with giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity.
	Proposed (if applicable): not applicable
Dosage in the EEA	Current: *Prevention of skeletal related events in adults with advanced malignancies involving bone* The recommended dose is 120 mg denosumab administered as a single subcutaneous injection once every 4 weeks into the thigh, abdomen or upper arm. Patients must be adequately supplemented with calcium and vitamin D.

	Giant cell tumour of bone The recommended dose is 120 mg denosumab administered as a single subcutaneous injection once every 4 weeks into the thigh, abdomen or upper arm with additional 120 mg doses on days 8 and 15 of treatment of the first month of therapy. Patients must be adequately supplemented with calcium and vitamin D.
	Proposed (if applicable): not applicable
Pharmaceutical form(s) and strengths	Current (if applicable): 120 mg solution for injection (70 mg/mL)
	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: 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 aims 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

YAXWER 120 mg solution for injection (Gedeon Richter Plc.) is demonstrated to be a biosimilar medicine to the reference product XGEVA 120 mg solution for injection (Amgen Europe B.V.) which has been authorised in the EU since 13 July 2011.

The safety concern list has been based on the European Risk Management Plan (v36.0, date: 11 December 2020) of the reference medicinal product, XGEVA. All important risks relevant for risk management were harmonised with those of XGEVA 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: Osteonecrosis of the jaw

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

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 higher incidence of ONJ among subjects treated with denosumab compared to zoledronic acid has been observed in skeletal related events (SRE) prevention clinical trials with the reference product. The highest incidence of ONJ was observed in a phase III trial in patients with multiple myeloma. In the double-blind treatment phase of this trial, ONJ was confirmed in 5.9% of patients treated with XGEVA (median exposure of 19.4 months; range 1 - 52) and in 3.2% of patients treated with zoledronic acid. At the completion of the double-blind treatment phase of

this trial, the patient-year adjusted incidence of confirmed ONJ in the XGEVA group (median exposure of 19.4 months; range 1 - 52), was 2.0 per 100 patient-years during the first year of treatment, 5.0 in the second year, and 4.5 thereafter. The median time to ONJ was 18.7 months (range: 1 - 44).

In the primary treatment phases of three phase III active-controlled clinical trials in patients with advanced malignancies involving bone, ONJ was confirmed in 1.8% of patients treated with XGEVA (median exposure of 12.0 months; range: 0.1 – 40.5) and 1.3% of patients treated with zoledronic acid. Clinical characteristics of these cases were similar between treatment groups. Among subjects with confirmed ONJ, most (81% in both treatment groups) had a history of tooth extraction, poor oral hygiene, and/or use of a dental appliance. Most subjects were receiving or had received chemotherapy.

A non-randomised, retrospective, observational study in 2,877 patients with cancer treated with XGEVA or zoledronic acid in Sweden, Denmark, and Norway showed that 5-year incidence proportions of medically confirmed ONJ were 5.7% (95% CI: 4.4, 7.3; median follow up time of 20 months [range 0.2-60]) in a cohort of patients receiving XGEVA and 1.4% (95% CI: 0.8, 2.3; median follow up time of 13 months [range 0.1-60]) in a separate cohort of patients receiving zoledronic acid. Five-year incidence proportion of ONJ in patients switching from zoledronic acid to XGEVA was 6.6% (95% CI: 4.2, 10.0; median follow up time of 13 months [range 0.2-60]).

The trials in patients with breast or prostate cancer included an XGEVA extension treatment phase (median overall exposure of 14.9 months; range: 0.1 – 67.2). ONJ was confirmed in 6.9% of patients with breast cancer and prostate cancer during the extension treatment phase.

The patient-year adjusted overall incidence of confirmed ONJ was 1.1 per 100 patient-years during the first year of treatment, 3.7 in the second year and 4.6 thereafter. The median time to ONJ was 20.6 months (range: 4 - 53).

In a phase III trial in patients with non-metastatic prostate cancer (a patient population for which XGEVA is not indicated), with longer treatment exposure of up to 7 years, the patient-year adjusted incidence of confirmed ONJ was 1.1 per 100 patient-years during the first year of treatment, 3.0 in the second year, and 7.1 thereafter.

In a long-term phase II open-label clinical trial in patients with giant cell tumour of bone, ONJ was confirmed in 6.8% of patients, including one adolescent (median number of 34 doses; range 4 – 116). At the completion of the trial, median time on trial including safety follow-up phase was 60.9 months (range: 0 – 112.6). The patient-year adjusted incidence of confirmed ONJ was 1.5 per 100 patient-years overall (0.2 per 100 patient-years during the first year of treatment, 1.5 in the second year, 1.8 in the third year, 2.1 in the fourth year, 1.4 in the fifth year, and 2.2 thereafter). The median time to ONJ was 41 months (range: 11 - 96).

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

Reversibility: ONJ is clinically reversible, treatment interruption or discontinuation can resolve the majority of the cases. Surgical treatment may be required; bone resection is not usually necessary.

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

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

Risk factors and risk groups:
Risk factors associated with ONJ include the use of antiresorptives (particularly aminobisphosphonates delivered by intravenous dosing), older age, poor dental hygiene, periodontal disease, invasive dental procedures, trauma from poorly fitting dentures, malignancy, chemotherapy (including antiangiogenesis agents such as bevacizumab), radiation to head and neck, corticosteroids, hypercoagulable state secondary to underlying malignancy, smoking and vascular insufficiency due to thrombosis (Almazrooa 2009; Estilo 2008; 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. This risk is preventable and treatable with the appropriate risk minimisation measures.

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 nonclinical 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 clinical trials and from post-marketing setting with the reference product.

Characterisation of the risk:
Frequency: In the clinical trials programme of the reference product, AFF has been reported uncommonly in patients treated with 120 mg and the risk increased with longer duration of treatment. Events have occurred during treatment and up to 9 months after treatment discontinued.

In the denosumab 120 mg clinical trials with the reference product, 15 subjects experienced 17 events meeting the American Society for Bone and Mineral Research criteria for AFF. This corresponds to 0.2% of all subjects who received at least one dose of denosumab. All of these

adjudicated events of AFF occurred in subjects who received denosumab 120 mg for at least 4 years corresponding to 0.7% of subjects who were followed for 4 or more years.

Severity: AFF is a medically important adverse event that generally requires significant medical interventions such as surgery and on-going monitoring to mitigate risk for and severity of contralateral fractures.

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

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

Impact on quality of life: 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 AFF. Corticosteroids have also been reported in the literature to potentially be associated with AFF (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 several months after the last dose in patients with giant cell tumour of bone and in patients with growing skeletons

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

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

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

- Hypercalcaemia may result from rapid resorption of retained primary spongiosa in a skeleton with active endochondral ossification such as in patients with growing skeleton. The rate of endochondral ossification and duration of exposure to denosumab would determine the amount of accumulated primary spongiosa that could influence the magnitude of resorptive response (mechanostat-driven) and release of calcium from the skeleton either near the growth plates (as can be the case with the young adult and adolescent patients) or from the giant cell tumours themselves that have partially ossified in the cases of the adult patients with tumour recurrence via an autocrine/paracrine mechanism.
- The magnitude of the resorptive response following treatment and withdrawal in the patients with GCTB and in those with an immature skeleton could be dictated by the normal high rate of bone turnover within the GCTB lesion in the growing skeleton of young patients.

The response of the osteoclast lineage to loss of inhibition of osteoclastogenesis may be intrinsically more robust in young individuals or may be affected by intratumor signalling pathways (e.g., parathyroid hormone-related protein) in GCTB.

Evidence source(s) and strength of evidence:
This risk was identified in clinical trials and from post-marketing setting with the reference product.

Characterisation of the risk:
Frequency: Based on 4 clinical cases, concerning 2 adults and 2 adolescents, identified from a completed clinical trial (study 20062004) with the reference product, the frequency of hypercalcaemia in patients with GCTB following discontinuation of XGEVA was 0.8 events per 100 subjects which correspond to an uncommon frequency (≥0.1 and <1 event per 100 subjects).

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

Severity: Above mentioned 4 cases were considered grade 2, 3, or 4 in severity. All subjects had acute renal injury, and all were hospitalised.

The severity of events in the post-marketing literature case reports appears qualitatively similar.

Reversibility: Hypercalcaemia is reversible with appropriate supportive therapy.

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

Impact on quality of life: Severe hypercalcaemia might require hospitalisation. Patients experiencing hypercalcaemia may develop complications, e.g., acute renal injury.

Risk factors and risk groups:
Patients with GCTB and young patients with growing skeletons following discontinuation of denosumab. In general, the most common cause of hypercalcaemia in humans is hyperparathyroidism, particularly among women and individuals aged 65 years or older (Minisola 2015). Hyperthyroidism and rhabdomyolysis associated with renal failure also increase the risk of

hypercalcaemia, as does the ingestion of large amounts of calcium through dairy products or more recently liberal use of calcium supplements (Machado 2015; Minisola 2015).

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

Impact on the risk-benefit balance of the product:
At severe levels, hypercalcaemia can lead to stupor or coma. Chronically high levels of hypercalcaemia can also cause calcium renal stones, pancreatitis and peptic ulcers. Routine pharmacovigilance activities further characterise the risk of hypercalcaemia.

Public health impact:
No significant public health impact is expected as hypercalcaemia several months after the last dose in patients with GCTB occurs uncommonly and GCTB is a rare tumour. Off-label use of denosumab in paediatric patients appears to be limited to rare conditions for which there is significant unmet medical need.

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

Characterisation of the risk:
Frequency: In the pooled pivotal SRE solid tumour studies with the reference product, subject's incidence of CV adverse events was 29.7% in both treatment groups; the hazard ratio was 0.98 (95% CI: 0.89, 1.08).

In a pivotal study with denosumab 120 mg (administered every 4 weeks) in subjects with castration resistant prostate cancer (Study 20050147), the subject incidence of CV adverse events was 33.1% in the denosumab group and 27.0% in the placebo group; the hazard ratio was 1.23 (95% CI: 1.01, 1.49).

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

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

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

Reversibility: No data on reversibility are available.

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

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

Risk factors and risk groups:
The denosumab development 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; Hak 2000).

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

Preventability:
Based on clinical data to date, denosumab has not been associated with an increased incidence or severity of CV adverse effects; therefore, no preventive measures are defined. Patients with potential CV events should be managed according to usual standards of care.

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

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

Important potential risk: Malignancy

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

Evidence source(s) and strength of evidence:
Imbalance was observed in the NPM events between the zoledronic acid and XGEVA (the reference product) treatment groups in the pivotal clinical studies. The results of Study 20170728, a post-marketing retrospective cohort study, showed NPM incidence rates for XGEVA were generally lower than those for zoledronic acid in unadjusted analyses, suggesting no obvious excess risk associated with XGEVA.

Characterisation of the risk:
Frequency: In the primary, double-blind treatment phases of 4 phase III active-controlled clinical trials with the reference product in patients with advanced malignancies involving bone, NPM was reported in 54/3,691 (1.5%) of patients treated with XGEVA (median exposure of 13.8 months; range: 1.0 to 51.7) and 33/3,688 (0.9%) of patients treated with zoledronic acid (median exposure of 12.9 months; range 1.0 to 50.8). The cumulative incidence at 1 year was 1.1% for denosumab and 0.6% for zoledronic acid, respectively.

In the SRE multiple myeloma study, the subject incidence of adverse events of NPM was 2.6% in the denosumab group and 1.4% in the zoledronic acid group; the hazard ratio was 1.81 (95% CI: 0.90, 3.66). Subjects who had new malignancy and no pattern was apparent in the types of new primary malignancies.

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

In study 20170728, a retrospective observational cohort study of 9,710 patients with bone metastases from breast, prostate, or lung cancer treated with XGEVA or IV zoledronic acid, the overall rate of NPM for the breast cancer cohort was 11.5 per 1,000 person-years of follow-up (PY) in the XGEVA group and 16.2 per 1,000 PY in the zoledronic acid group; for the prostate cancer cohort was 19.6 per 1,000 PY in the XGEVA group and 10.1 per 1,000 PY in the zoledronic acid group; and for the lung cancer cohort was 9.5 per 1,000 PY in the XGEVA group and 11.5 per 1,000 PY in the zoledronic acid group.

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

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

Severity: Not applicable.

Reversibility: No data on reversibility are available.

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

Impact on quality of life: Malignancy is typically disabling and may require surgery, chemotherapy, and/or radiotherapy.

Risk factors and risk groups:
General factors for increasing risk of new primary malignancy include advancing age, diet, cigarette smoking, excessive ethanol consumption, and numerous environmental toxins. In addition, advanced cancer populations are at increased risk for NPM because of their existing malignancy, possible genetic predisposition, and exposure to chemotherapy and radiation treatment.

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

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

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

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

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

Evidence source(s) and strength of evidence:
The risk of delay in diagnosis of primary malignancy in giant cell tumour of bone is a regulatory concern based on difficulties in diagnosing primary malignancy in giant cell tumour of bone (PMGCTB). This safety concern was identified in the clinical trial setting with the reference product.

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

Severity: Not applicable.

Reversibility: Not applicable.

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

Impact on quality of life: Malignancy is typically disabling and may require surgery, chemotherapy, and/or radiotherapy.

Risk factors and risk groups:
Patients with GCTB are known to be at risk for PMGCTB.

Preventability:
No preventive measures are known.

Impact on the risk-benefit balance of the product:
Not known.

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

Important potential risk: Hypercalcaemia several months after the last dose in patients other than those with giant cell tumour of bone or growing skeletons

Potential mechanisms:
The pathogenesis of hypercalcaemia several months after the last dose in patients other than those with GCTB or growing skeletons may be a consequence of the transient increase in bone turnover activity. Upon cessation of denosumab, the disinhibition or RANKL allows for terminal differentiation and activation of osteoclasts, which were suppressed during treatment. In patients with underlying causes for calcium dyscrasias (i.e., subclinical hyperparathyroidism), denosumab discontinuation, with its transient increase in bone remodelling and accompanying release of bone mineral, could theoretically be associated with transient hypercalcaemia in susceptible individuals if the normal homeostatic mechanism regulating serum calcium are not appropriately maintained.

Evidence source(s) and strength of evidence:
Hypercalcaemia several months after the last dose in patients other than those with GCTB or growing skeletons is a theoretical concern based on the identified risk in other specific populations, GCTB, and paediatric populations.

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

Severity: Not applicable.

Reversibility: No data on reversibility are available.

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

Impact on quality of life: Patients may present with severe hypercalcaemia requiring hospitalisation. Patients who experience hypercalcaemia may develop complications such as acute renal injury.

Risk factors and risk groups:
Patients other than those with GCTB or growing skeletons following cessation of denosumab 120 mg.

Preventability:
No preventive measures are known.

Impact on the risk-benefit balance of the product:
Not known.

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

SVII.3.2. Presentation of the missing information

Patients with prior intravenous bisphosphonate treatment

Evidence source:
The incidence of ONJ in patients with prior intravenous bisphosphonate use was similar to that of patients who only received XGEVA in the completed Study 20101363 of Amgen. No notable association was evident between ONJ and prior use of bisphosphonates.

Population in need of further characterisation:
There is information from studies with the reference product in patients with cancer showing that there is no increased risk of serious complications caused by bone metastases in patients who received XGEVA following treatment with bisphosphonates. However, more information is needed.

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

Evidence source:
The overall safety profile of the reference product, XGEVA in the completed Study 20062004 of Amgen was similar to the safety profile of XGEVA observed in the treatment of subjects with advanced cancer and bone metastases.

Population in need of further characterisation:
Information on safety with long-term treatment and with long-term follow-up in adults or adolescents with GCTB will be monitored by routine pharmacovigilance activities.

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

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

Population in need of further characterisation:
Information is not available on safety in patients with GCTB that is resectable where resection is unlikely to result in severe morbidity.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Osteonecrosis of the jaw Atypical femoral fracture Hypercalcaemia several months after the last dose in patients with giant cell tumour of bone and in patients with growing skeletons
Important potential risks	Cardiovascular events Malignancy Delay in diagnosis of primary malignancy in giant cell tumour of bone Hypercalcaemia several months after the last dose in patients other than those with giant cell tumour of bone or growing skeletons
Missing information	Patients with prior intravenous bisphosphonate treatment Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumour of bone Off-label use in patients with giant cell tumour of bone that is resectable where resection is unlikely to result in severe morbidity

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

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires:

Targeted follow-up questionnaires, in line with the originator, are summarised in table below.

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

Targeted follow-up questionnaire	Safety concern	Purpose
Osteonecrosis of the jaw	Osteonecrosis of the jaw	To monitor the nature of ONJ
Atypical fractures	Atypical femoral fracture	To monitor the nature of AFF

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	
Osteonecrosis of the jaw	Routine risk communication: *SmPC sections 4.3, 4.4, 4.8 and 5.1* *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: *restricted medical prescription*
Atypical femoral fracture	Routine risk communication: *SmPC sections 4.4 and 4.8* *PL sections 2 and 4* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Recommendation for reporting potential symptoms is provided in SmPC section 4.4* Other risk minimisation measures beyond the Product Information: Legal status: *restricted medical prescription*
Hypercalcaemia several months after the last dose in patients with giant cell tumour of bone and in patients with growing skeletons	Routine risk communication: *SmPC sections 4.4 and 4.8* *PL sections 2 and 4* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Recommendation regarding monitoring of calcium levels periodically after treatment discontinuation is provided in SmPC section 4.4* Other risk minimisation measures beyond the Product Information: Legal status: *restricted medical prescription*

Safety concern	Routine risk minimisation activities
Important potential risk	
Cardiovascular events	Routine risk communication: *None.* Other risk minimisation measures beyond the Product Information: Legal status: *restricted medical prescription*
Malignancy	Routine risk communication: *SmPC sections 4.4, 4.8 and 5.1* *PL section 4* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Recommendation regarding monitoring of radiological signs of malignancy, new radiolucency or osteolysis is provided in SmPC section 4.4* Other risk minimisation measures beyond the Product Information: Legal status: *restricted medical prescription*
Delay in diagnosis of primary malignancy in giant cell tumour of bone	Routine risk communication: *None.* Other risk minimisation measures beyond the Product Information: Legal status: *restricted medical prescription*
Hypercalcaemia several months after the last dose in patients other than those with giant cell tumour of bone or growing skeletons	Routine risk communication: *None.* Other risk minimisation measures beyond the Product Information: Legal status: *restricted medical prescription*
Missing information	
Patients with prior intravenous bisphosphonate treatment	Routine risk communication: *SmPC sections 4.5 and 5.1* *PL section 2* Other risk minimisation measures beyond the Product Information: Legal status: *restricted medical prescription*
Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumour of bone	Routine risk communication: *None.* Other risk minimisation measures beyond the Product Information: Legal status: *restricted medical prescription*
Off-label use in patients with giant cell tumour of bone that is resectable where resection is unlikely to result in severe morbidity	Routine risk communication: *None.* Other risk minimisation measures beyond the Product Information: Legal status: *restricted 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 YAXWER 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 YAXWER 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 YAXWER. QR code to this website is placed within the Patient information leaflet and on the outer packaging of YAXWER.

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		
Osteonecrosis of the jaw	Routine risk minimisation measures *SmPC section 4.4, where guidance on oral hygiene and dental management is provided* *SmPC sections 4.3, 4.8 and 5.1* *PL sections 2 and 4*	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
	Legal status: *restricted medical prescription* Additional risk minimisation measures *Patient card*	
Atypical femoral fracture	Routine risk minimisation measures *SmPC section 4.4, where recommendation for reporting potential symptoms is provided* *SmPC section 4.8* *PL sections 2 and 4* Legal status: *restricted medical prescription* Additional risk minimisation measures *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *AE follow-up questionnaire for osteonecrosis of the jaw* Additional pharmacovigilance activities *None*
Hypercalcaemia several months after the last dose in patients with giant cell tumour of bone and in patients with growing skeletons	Routine risk minimisation measures *SmPC section 4.4, where recommendation regarding monitoring of calcium levels periodically after treatment discontinuation is provided* *SmPC section 4.8* *PL sections 2 and 4* Legal status: *restricted medical prescription* Additional risk minimisation measures *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities *None*
Important potential risks		
Cardiovascular events	Routine risk minimisation measures Legal status: *restricted medical prescription* Additional risk minimisation measures *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities *None*
Malignancy	Routine risk minimisation measures *SmPC section 4.4, where recommendation regarding monitoring of radiological signs of malignancy, new*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities *None*

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	radiolucency or osteolysis is provided *SmPC sections 4.8 and 5.1* *PL section 4* Legal status: *restricted medical prescription* Additional risk minimisation measures *None*	
Delay in diagnosis of primary malignancy in giant cell tumour of bone	Routine risk minimisation measures Legal status: *restricted medical prescription* Additional risk minimisation measures *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities *None*
Hypercalcaemia several months after the last dose in patients other than those with giant cell tumour of bone or growing skeletons	Routine risk minimisation measures Legal status: *restricted medical prescription* Additional risk minimisation measures *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities *None*
Missing information		
Patients with prior intravenous bisphosphonate treatment	Routine risk minimisation measures Legal status: *restricted medical prescription* Additional risk minimisation measures *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities *None*
Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumour of bone	Routine risk minimisation measures Legal status: *restricted medical prescription* Additional risk minimisation measures *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities *None*
Off-label use in patients with giant cell tumour	Routine risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Safety concern	Risk minimisation measures	Pharmacovigilance activities
of bone that is resectable where resection is unlikely to result in severe morbidity	Legal status: *restricted medical prescription* Additional risk minimisation measures *None*	*None* Additional pharmacovigilance activities *None*

Part VI: Summary of the risk management plan

Summary of risk management plan for YAXWER (denosumab)

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

I. The medicine and what it is used for

YAXWER 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 YAXWER's benefits can be found in YAXWER'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 YAXWER, together with measures to minimise such risks and the proposed studies for learning more about YAXWER'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 YAXWER, 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 YAXWER is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of YAXWER 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 YAXWER. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	Osteonecrosis of the jaw Atypical femoral fracture Hypercalcaemia several months after the last dose in patients with giant cell tumour of bone and in patients with growing skeletons
Important potential risks	Cardiovascular events Malignancy Delay in diagnosis of primary malignancy in giant cell tumour of bone Hypercalcaemia several months after the last dose in patients other than those with giant cell tumour of bone or growing skeletons
Missing information	Patients with prior intravenous bisphosphonate treatment Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumour of bone Off-label use in patients with giant cell tumour of bone that is resectable where resection is unlikely to result in severe morbidity

II.B Summary of important risks

Important identified risk: Osteonecrosis of the jaw	
Evidence for linking the risk to the medicine	This risk was identified in clinical trials and from post-marketing setting with the reference product.
Risk factors and risk groups	Risk factors associated with osteonecrosis of the jaw include the use of antiresorptives (particularly aminobisphosphonates delivered by intravenous dosing), older age, poor dental hygiene, periodontal disease, invasive dental procedures, trauma from poorly fitting dentures, malignancy, chemotherapy (including antiangiogenesis agents such as bevacizumab), radiation to head and neck, corticosteroids, hypercoagulable state secondary to underlying malignancy, smoking and vascular insufficiency due to thrombosis (Almazrooa and Woo,

	2009[1]; Estilo, 2008[2]; Mehrotra and Ruggiero, 2006[3]; Ruggiero, 2006[4]).
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.4, where guidance on oral hygiene and dental management is provided* *SmPC sections 4.3, 4.8 and 5.1* *PL sections 2 and 4* Legal status: *restricted medical prescription* Additional risk minimisation measures *Patient card*

Important identified risk: Atypical femoral fracture	
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	Long-term antiresorptive treatment has been associated with atypical femoral fracture (AFF). Corticosteroids have also been reported in the literature to potentially be associated with AFF (Meier, 2012[5]; Giusti, 2011[6]). 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[7]).
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* Legal status: *restricted medical prescription* Additional risk minimisation measures *None*

[1] *Almazrooa SA, Woo SB. Bisphosphonate and nonbisphosphonate-associated osteonecrosis of the jaw: a review. J Am Dent Assoc. 2009 Jul;140(7):864-75. doi: 10.14219/jada.archive.2009.0280.*

[2] *Estilo CL, Fornier M, Farooki A, Carlson D, Bohle G 3rd, Huryn JM. Osteonecrosis of the jaw related to bevacizumab. J Clin Oncol. 2008 Aug 20;26(24):4037-8. doi: 10.1200/JCO.2007.15.5424.*

[3] *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.*

[4] *Ruggiero S, Gralow J, Marx RE, Hoff AO, Schubert MM, Huryn JM et al; Practical guidelines for the prevention, diagnosis, and treatment of osteonecrosis of the jaw in patients with cancer. J Oncol Pract. 2006 Jan;2(1):7-14. doi: 10.1200/JOP.2006.2.1.7.*

[5] *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.*

[6] *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.*

[7] *Shane E, Burr D, Ebeling PR, Abrahamsen B, Adler RA, Brown TD et al; 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 several months after the last dose in patients with giant cell tumour of bone and in patients with growing skeletons	
Evidence for linking the risk to the medicine	This risk was identified in clinical trials and from post-marketing setting with the reference product.
Risk factors and risk groups	Patients with giant cell tumour of bone and young patients with growing skeletons following discontinuation of denosumab. In general, the most common cause of hypercalcaemia in humans is hyperparathyroidism, particularly among women and individuals aged 65 years or older (Minisola, 2015 [8]). Hyperthyroidism and rhabdomyolysis associated with renal failure also increase the risk of hypercalcaemia, as does the ingestion of large amounts of calcium through dairy products or more recently liberal use of calcium supplements (Machado, 2015[9]; Minisola, 2015[8]).
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.4, where recommendation regarding monitoring of calcium levels periodically after treatment discontinuation is provided* *SmPC section 4.8* *PL sections 2 and 4* Legal status: *restricted medical prescription* Additional risk minimisation measures *None*

Important potential risk: Cardiovascular events	
Evidence for linking the risk to the medicine	The risk of cardiovascular events is a regulatory concern based on the epidemiological association between osteoprotegerin (OPG) levels and cardiovascular disease in man. Clinical data have not substantiated a cause-and-effect between OPG and atherosclerotic processes nor between denosumab or inhibition of RANKL and undesirable cardiovascular outcomes
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[10]; Hak, 2000[11]).

[8] Minisola S, Pepe J, Piemonte S, Cipriani C. The diagnosis and management of hypercalcaemia. BMJ. 2015 Jun 2;350:h2723. doi: 10.1136/bmj.h2723.

[9] Machado MC, Bruce-Mensah A, Whitmire M, Rizvi AA. Hypercalcemia Associated with Calcium Supplement Use: Prevalence and Characteristics in Hospitalized Patients. J Clin Med. 2015 Mar 9;4(3):414-24. doi: 10.3390/jcm4030414.

[10] Pract. 2006 Jan;2(1):7-14. doi: 10.1200/JOP.2006.2.1.7.

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.

[11] 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.

Important potential risk: Cardiovascular events	
Risk minimisation measures	Routine risk minimisation measures Legal status: *restricted medical prescription* Additional risk minimisation measures *None*

Important potential risk: Malignancy	
Evidence for linking the risk to the medicine	Imbalance was observed in the new primary malignancy (NPM) events between the zoledronic acid and XGEVA (the reference product) treatment groups in the pivotal clinical studies. The results of Study 20170728, a post-marketing retrospective cohort study, showed NPM incidence rates for XGEVA were generally lower than those for zoledronic acid in unadjusted analyses, suggesting no obvious excess risk associated with XGEVA.
Risk factors and risk groups	General factors for increasing risk of new primary malignancy include advancing age, diet, cigarette smoking, excessive ethanol consumption, and numerous environmental toxins. In addition, advanced cancer populations are at increased risk for NPM because of their existing malignancy, possible genetic predisposition, and exposure to chemotherapy and radiation treatment
Risk minimisation measures	Routine risk minimisation measures Legal status: *restricted medical prescription* Additional risk minimisation measures *None*

Important potential risk: Delay in diagnosis of primary malignancy in giant cell tumour of bone	
Evidence for linking the risk to the medicine	The risk of delay in diagnosis of primary malignancy in giant cell tumour of bone is a regulatory concern based on difficulties in diagnosing primary malignancy in giant cell tumour of bone (PMGCTB). This safety concern was identified in the clinical trial setting with the reference product.
Risk factors and risk groups	Patients with giant cell tumour of bone are known to be at risk for PMGCTB.
Risk minimisation measures	Routine risk minimisation measures Legal status: *restricted medical prescription* Additional risk minimisation measures *None*

Important potential risk: Hypercalcaemia several months after the last dose in patients other than those with giant cell tumour of bone or growing skeletons	
Evidence for linking the risk to the medicine	Hypercalcaemia several months after the last dose in patients other than those with GCTB or growing skeletons is a theoretical concern based on the identified risk in other specific populations, GCTB and paediatric populations.
Risk factors and risk groups	Patients other than those with GCTB or growing skeletons following cessation of denosumab 120 mg.
Risk minimisation measures	Routine risk minimisation measures Legal status: *restricted medical prescription* Additional risk minimisation measures *None*

II.C Post-authorisation development plan

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

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

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

There are no studies required for YAXWER.

[redacted]

Annex 4 - Specific adverse drug reaction follow-up forms

Table of contents

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. _____	

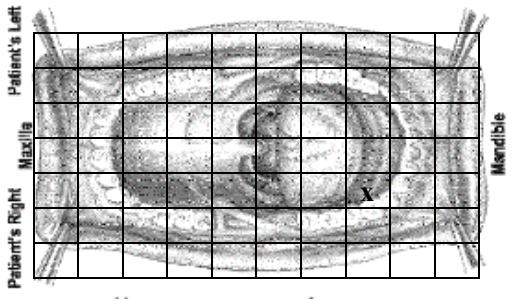
PATIENT DETAILS			
Patient initials:	____	Gender:	☐ Male / ☐ Female
Year of birth:	_____	Age at time of event:	____
Height:	____ ☐ cm / ☐ in	Weight:	____ ☐ kg / ☐ lbs
Ethnic origin:	☐ Caucasian / ☐ Asian / ☐ Black / ☐ Other: ____		

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): ☐ Right maxilla, teeth and lateral jaw	Please indicate the location of involved area(s) on the picture below (mark site(s) clearly with 'X').

☐ 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 ☐ Unknown Date of examination: __/__/____ *(dd/mm/yyyy)*
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 consumption:	☐ Yes ☐ No ☐ Unknown If yes, estimated drinks per week: _____
Diabetes:	☐ Yes ☐ No ☐ Unknown

	If yes: ☐ Type I ☐ Type II

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	

[redacted]

Annex 6 - Details of proposed additional risk minimisation activities

Key messages of the additional risk minimisation measures

Patient card

Patient cards for Osteonecrosis of the jaw will be distributed to prescribers of YAXWER 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 (YAXWER) injections for cancer-related conditions, including:

- The risk of osteonecrosis of the jaw during treatment with YAXWER;
- 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 YAXWER 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]