EU [redacted] Risk Management Plan

for

Osvyrti 60 mg solution for injection in pre-filled syringe

(Denosumab)

RMP version to be assessed as part of this application:

RMP Version number	1.0
Data lock point for this RMP	01-Feb-2024
Date of final sign off	22-Feb-2024

Rationale for submitting an updated RMP: Not applicable for initial marketing authorisation application submission.

Summary of significant changes in this RMP: Not Applicable

Other RMP versions under evaluation: Not applicable

QPPV name: Agata Gesiewicz

QPPV signature: [redacted]

[redacted]

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[redacted]

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Part I: Product(s) Overview

Table 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 mineralization (M05BX04)
Marketing Authorisation Applicant	Accord Healthcare S. L.U.
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA) [redacted]	Osvyrti 60 mg solution for injection in pre-filled syringe
Marketing authorisation procedure	Centralised Procedure (H0006399) [redacted]
Brief description of the product	<u>Chemical class:</u> Monoclonal antibody
	<u>Summary of mode of action:</u> Denosumab is a human monoclonal antibody (IgG2) that targets and binds with high affinity and specificity to 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.
	<u>Important information about its composition</u>

[redacted]

	Osvyrti 60 mg solution for injection in pre-filled syringe Each pre-filled syringe contains 60 mg of denosumab in 1 mL of solution (60 mg/mL) Excipient with known effect This medicine contains 46 mg sorbitol in each mL of solution
Hyperlink to the Product Information	Refer Module 1.3.1 for SmPC and PIL.
Indication(s) in the EEA	***Current*** Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures. In postmenopausal women denosumab significantly reduces the risk of vertebral, non-vertebral and hip fractures. 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, denosumab 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.
Dosage in the EEA	***Current*** Posology 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. The optimal total duration of antiresorptive treatment for osteoporosis (including both denosumab and bisphosphonates) has not been established. The need for continued treatment should

	be re-evaluated periodically based on the benefits and potential risks of denosumab on an individual patient basis, particularly after 5 or more years of use. **Method of administration:** For subcutaneous use. Administration should be performed by an individual who has been adequately trained in injection techniques.
Pharmaceutical form(s) and strengths	***Current*** Solution for injection in pre-filled syringe 60 mg.
Is the product subject to additional monitoring in the EU[redacted]?	No

[redacted]

Part II: Safety specification

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

Not Applicable

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

There were no non-clinical studies performed for Osvyrti 60 mg solution for injection in pre-filled syringe.

Part II: Module SIII - Clinical trial exposure

Brief overview of development:

Denosumab of Intas is biosimilar denosumab candidate under development by Intas Pharmaceutical Limited (Biopharma Division). Denosumab of Intas is already approved by Indian drug licensing authority- Drug Controller General (India) for marketing in Indian population since 2018.

Osvyrti PFS (containing 60 mg of denosumab in 1 mL of solution) has been developed as a proposed biosimilar to both the US-licensed and EU-approved Prolia. Consistent with biosimilar guidance which were current at the time of product development, the development program for Osvyrti PFS as a proposed biosimilar to Prolia, includes a comprehensive comparative analytical similarity assessment program to Prolia, comparing Pharmacokinetics, Pharmacodynamics, and Immunogenicity assessment of Denosumab in Phase III study conducted in postmenopausal women with osteoporosis between the ages of 55 to 90 years. Details of the clinical program are provided in Table 2 below:

Clinical Trial Exposure:

The Test Product-T (Denosumab 60 mg/mL) or Reference Product-R (Prolia® 60 mg/mL) was administered twice during the treatment (main) phase of this study as subcutaneous injection on Visit-2 (Day 1 ± 3) and on Visit-9 (Day 181 ± 14) to the patients in treatment period as per randomization schedule based on an algorithm implemented in the interactive web response system (IWRS).

Further, Test Product-T or Reference Product-R was administered as subcutaneous injection on Visit-16 (Any day within 21 days after EOS visit ± 5) (in transition-extension period) to the patients

who (a) were randomized in reference arm AND (b) had completed PK assessments during 12-month treatment period.

Table 2: Clinical studies with Denoaumab PFS

Clinical Study Design	Study treatment	Comment
Phase III A Randomized, Double-Blind, Active-Controlled, Parallel Arm, Multicenter study Comparing Pharmacokinetics, Pharmacodynamics, and Immunogenicity of Denosumab of Intas Pharmaceutical Limited (60 mg/mL) with Prolia® in Postmenopausal Women with Osteoporosis	**Test product**: Denosumab solution for injection in single-use prefilled syringe 60mg/mL. **Reference product:** Prolia® solution for injection in single-use prefilled syringe (Denoaumab)	**Study site:** Multiple sites in India (Andhra Pradesh, Chhattisgarh, Gujarat, Karnataka, Maharashtra, New Delhi, Odisha, Rajasthan, Telangana) and Georgia. **Study status:** Completed **Treatment Period:** A total of 552 patients [Test Arm = 276 patients; Reference Arm = 276 patients] were randomized and dosed treatment period in the study. Out of 552 enrolled patients, a total of 464 patients [Test Arm = 236 patients; Reference Arm = 228 patients] completed the main phase (12-months of treatment duration) of the study. **Transition-extension Period:** A total of 123 patients [Test Arm = 62 patients; Reference Arm = 61 patients] were rerandomized and dosed in Transition-extension Period of the study. Out of 123 enrolled patients, a total of 121 patients [Test Arm = 62 patients; Reference Arm = 61 patients] completed Transition-extension Period of the study.

Treatment Period:

The mean age for the 552 patients was 63 ± 6.3 years. Of total 552 patients, 522 (94.6%) patients were Indian and 30 (5.4%) patients were Georgian. The age of 359 (65.0%) patients

was <65 and the age of 193 (35.0%) patients was ⩾ 65. The mean weight was 60.9 ± 8.10 kg. The mean BMI was 26.80 ± 3.433 kg/m^2. (Safety Set, ITT Set).

Demographic details are presented in below table.

Table 3. Subject Demographic data and baseline characteristics (Safety set, Main Phase)

		Statistics	Denosumab (N=276)	Prolia (N=276)	Total (N=552)	p-value
Age (years)		n	276	276	552	0.5395
		Mean (SD)	63 (6.1)	63 (6.5)	63 (6.3)	
		Median	61	61	61	
		Min, Max	55, 88	55, 86	55, 88	
Age Group	<65	n (%)	181 (65.6)	178 (64.5)	359 (65.0)	0.7889
	>=65	n (%)	95 (34.4)	98 (35.5)	193 (35.0)	
Gender	Female	n (%)	276 (100.0)	276 (100.0)	552 (100.0)	NE
Race	Asian	n (%)	261 (94.6)	261 (94.6)	552 (94.6)	1.0000
	American Indian or Alaska Native	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Black or African American	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Native Hawaiian	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Pacific Islander	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	White	n (%)	15 (5.4)	15 (5.4)	30 (5.4)	
	Other	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity	Not Hispanic Or Latino	n (%)	276 (100.0)	276 (100.0)	552 (100.0)	NE
	Hispanic or Latino	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Unknown	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Country	India	n (%)	261 (94.6)	261 (94.6)	522 (94.6)	1.0000
	Georgia	n (%)	15 (5.4)	15 (5.4)	30 (5.4)	
Weight (kg)		n	276	276	552	0.2749
		Mean (SD)	60.5 (7.91)	61.3 (8.28)	60.9 (8.10)	
		Median	59.5	60.0	60.0	
		Min, Max	50.0, 89.9	50.0, 88.6	50.0, 89.9	
Height (cm)		n	276	276	552	0.9553
		Mean (SD)	151 (6.4)	151 (6.2)	151 (6.3)	
		Median	150	150	150	
		Min, Max	133, 170	136, 172	133, 172	
BMI (kg/m²)		n	276	276	552	
		Mean (SD)	26.62 (3.079)	26.99 (3.751)	26.80 (3.433)	
		Median	26.49	26.45	26.48	
		Min, Max	20.55, 36.94	18.24, 40.45	18.24, 40.45	
Prior osteoporosis	Present	n (%)	7 (2.5)	7 (2.5)	14 (2.5)	1.0000
	Absent	n (%)	269 (97.5)	269 (97.5)	538 (97.5)	

[redacted]

		Statistics	Denosumab (N=276)	Prolia (N=276)	Total (N=552)	p-value
treatment status						

n = Number of patients in respective categories.

N = Number of patients in respective treatment arm.

Percentages are calculated based on the total number of patients in respective treatment arm.

For categorical data, p-value is calculated using a chi-square test. If any cell has expected counts less than 5, then the Fisher's exact test is used instead.

NE: Not Evaluable

Transition-extension Period:

The mean age for the 123 patients was 62 ± 6.2 years. All 123 (100%) patients were Indian. The age of 87 (70.7%) patients was <65 and the age of 36 (29.3%) patients was ≥ 65. The mean weight was 60.0 ± 7.52 kg. The mean BMI was 26.58 ± 3.572 kg/m^2. (Safety Set, ITT Set, PK Set, PD Set).

Table 4. Subject Demographic data and baseline characteristics (Extension Phase, Safety set)

		Statistics	Denosumab (N=62)	Prolia (N=61)	Total (N=123)	p-value
Age (Years)		n	62	61	123	0.9908
		Mean(SD)	62 (5.9)	62 (6.5)	62 (6.2)	
		Median	60	59	60	
		Min, Max	55, 79	55, 81	55, 81	
Age Group	>=65	n (%)	19 (30.6)	17 (27.9)	36 (29.3)	<0.0001
	<65	n (%)	43 (69.4)	44 (72.1)	87 (70.7)	
Gender	Female	n (%)	62 (100.0)	61 (100.0)	123 (100.0)	NE
Race	Asian	n (%)	62 (100.0)	61 (100.0)	123 (100.0)	NE
	American Indian or Alaska Native	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	
	Black or African American	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	
	Native Hawaiian	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	
	Pacific Islander	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	
	White	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	
	Other	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	
Ethnicity	Not Hispanic Or Latino	n (%)	62 (100.0)	61 (100.0)	123 (100.0)	NE
	Hispanic or Latino	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	
	Not Reported	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	
	Unknown	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	
Country	India	n (%)	62 (100.0)	61 (100.0)	123 (100.0)	NE
	Georgia	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	

		Statistics	Denosumab (N=62)	Prolia (N=61)	Total (N=123)	p-value
Weight (kg)		n	62	61	123	0.5664
		Mean(SD)	59.6 (7.11)	60.4 (7.95)	60.0 (7.52)	
		Median	59.8	60.0	60.0	
		Min, Max	50.0, 74.6	50.0, 78.9	50.0, 78.9	
Height (cm)		n	62	61	123	0.2543
		Mean(SD)	150 (5.4)	151 (7.0)	150 (6.2)	
		Median	149	150	149	
		Min, Max	138, 168	136, 166	136, 168	
BMI (kg/m²)		n	62	61	123	0.9121
		Mean(SD)	26.62 (3.388)	26.54 (3.777)	26.58 (3.572)	
		Median	26.52	25.99	26.14	
		Min, Max	20.90, 34.66	18.24, 36.99	18.24, 36.99	
Prior osteoporosis treatment status	Present	n (%)	1 (1.6)	1 (1.6)	2 (1.6)	0.0163
	Absent	n (%)	61 (98.4)	60 (98.4)	121 (98.4)	

Extent of Exposure:

Total 552 randomised patients were included in Treatment Period of the study and 123 patients were re-randomized in Transition-extension Period of the study.

Product Type	Test Arm (T)	Reference Arm (R)
Exposure	Denosumab Solution for Injection in Single use Prefilled syringe (60 mg/mL)	Prolia® Solution for injection in single-use prefilled syringe (60 mg/mL)
Treatment Period:		
Number of patients (N)	276	276
Transition-extension Period:		
Number of patients (N)	62	61

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

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

Table 5 Important Exclusion criteria in pivotal clinical studies within the development

programme

Important exclusion criteria	Reason for Exclusion	Is it considered to be included as missing information?	Rationale (if not include as missing information) or reason for exclusion
Phase III (Protocol No. 0774-19)			
1. Documented medical history of any of the following conditions: • metabolic or bone disease (except osteoporosis) that may interfere with the interpretation of the results, such as Paget's disease, osteomalacia, osteogenesis imperfecta, osteopetrosis, rheumatoid arthritis, ankylosing spondylitis or any other joint disease limiting mobility, Cushing's disease, hyperprolactinemia, malabsorption syndrome. • Any history of external beam or implant	Standard exclusion criteria as per study protocol	No	These conditions could potentially interfere with the aim/ objective of the study or it can have impact on patient safety.

[redacted]

Important exclusion criteria	Reason for Exclusion	Is it considered to be included as missing information?	Rationale (if not include as missing information) or reason for exclusion
radiation therapy involving the skeleton • History and /or presence of 1 severe fracture or 2 moderate vertebral fractures • Patients with bone metastases or a history of malignancies affecting bones • Smokers or who have smoked within last 06 months prior to start of the study • Major surgery, (e.g. requiring general anesthesia) within 12 weeks before screening, or will not have fully recovered from surgery, or has surgery planned during the time the participant is expected to participate in the study			

[redacted]

Important exclusion criteria	Reason for Exclusion	Is it considered to be included as missing information?	Rationale (if not include as missing information) or reason for exclusion
• Hepatitis B surface antigen (HBsAg) or hepatitis C antibody (anti-HCV) positive, or other clinically active liver disease, or tests positive for HBsAg or anti-HCV at Screening • Human immunodeficiency virus (HIV) antibody positive, or tests positive for HIV at Screening • Drug or alcohol abuse according to Diagnostic and Statistical Manual of Mental Disorders (5th edition) (DSM-V) criteria within 1 year before Screening. • Lymphoma, leukemia, or any malignancy (current or suspected) within the past 5 years except for basal cell or			

[redacted]

Important exclusion criteria	Reason for Exclusion	Is it considered to be included as missing information?	Rationale (if not include as missing information) or reason for exclusion
squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years; carcinoma in situ of the cervix; or malignancy, which is considered cured with minimal risk of recurrence • QTc interval >470 msec or QT interval >480 msec in participants with bundle branch block.			
2. Documented medical history of known allergies, hypersensitivity, or intolerance to denosumab or its excipients and history of any prior use of denosumab.	Standard exclusion criteria as per study protocol	No	Osvyrty is contraindicated in patients with hypersensitivity to denosumab or to any of the excipients. These conditions could potentially interfere with the aim/ objective of the study or it can

[redacted]

Important exclusion criteria	Reason for Exclusion	Is it considered to be included as missing information?	Rationale (if not include as missing information) or reason for exclusion
			have impact on patient safety.
3. Documented medical history and/or current evidence of any of the following oral/dental conditions: a) Prior history or current evidence of osteomyelitis or osteonecrosis of the jaw. b) Active dental or jaw condition which requires oral surgery. c) Planned invasive dental procedure expected during study period. d) Current evidence non-healed dental or oral surgery. e) Current evidence of poor oral hygiene. f) Ill-fitting denture	Standard exclusion criteria as per study protocol	No	These conditions could potentially interfere with the aim/ objective of the study, or it can have impact on patient safety.

Important exclusion criteria	Reason for Exclusion	Is it considered to be included as missing information?	Rationale (if not include as missing information) or reason for exclusion
4. Current hyper- or hypocalcemia, defined as albumin-adjusted serum calcium outside the normal range at screening. Serum calcium levels may be retested once in case of an elevated/low serum calcium level as assessed by the clinical laboratory. Final decision to include the patient based on the risk of hypocalcemia to be taken by the Investigator **5.** History of frequent occurrence of hypocalcemia, history of severe hypocalcemia or presence of diseases that can precipitate hypocalcemia frequently (like malabsorption syndromes (for	Standard exclusion criteria as per study protocol	No	These conditions could potentially interfere with the aim/ objective of the study or it can have impact on patient safety.

Important exclusion criteria	Reason for Exclusion	Is it considered to be included as missing information?	Rationale (if not include as missing information) or reason for exclusion
example celiac disease, history of excision of small intestine etc.) and severe renal impairment). **6.** Current, uncontrolled hyper- or hypoparathyroidism and history of hypoparathyroidism, per participant report or chart review. PTH outside the normal range (15-65 pg/mL) as assessed by central laboratory. **7.** Current, uncontrolled hyper- or hypothyroidism, defined as thyroid stimulating hormone outside of the normal range (TSH-0.465 to 4.68 mIU/L) at screening **8.** 25 (OH) Vitamin D lower than 20 ng/mL as			

Important exclusion criteria	Reason for Exclusion	Is it considered to be included as missing information?	Rationale (if not include as missing information) or reason for exclusion
assessed by the central laboratory at Screening. Vitamin D repletion will be permitted, and participants may be rescreened once			
9. Documented past/concomittent drug history of any of the following: • Administration of bisphosphonate as follows: - a) IV Bisphosphonate in the past 3 years. b) Oral bisphosphonates treatment for osteoporosis: i. More than 3 years of cumulative use ii. Any dose received within 6 months prior to randomization iii. More than 1	Standard exclusion criteria as per study protocol	No	These conditions could potentially interfere with the aim/ objective of the study or it can have impact on patient safety.

Important exclusion criteria	Reason for Exclusion	Is it considered to be included as missing information?	Rationale (if not include as missing information) or reason for exclusion
month of cumulative use between 6 and 12 months prior to randomization • Teriparatide or any PTH analogs treatment received within 12 months prior to randomization • Systemic oral or transdermal estrogen, SERMs, or calcitonin treatment of more than 1 month of cumulative use within 6 months prior to randomization • Androgen deprivation or hormonal ablation therapy of more than 1 month of cumulative use within 6 months			

Important exclusion criteria	Reason for Exclusion	Is it considered to be included as missing information?	Rationale (if not include as missing information) or reason for exclusion
prior to randomization • Tibolone or cinacalcet treatment received within 3 months prior to randomization • Systemic glucocorticoids: ≥ 5 mg prednisone equivalent per day for more than 10 days within 3 months prior to randomization • Taken any prohibited therapies, Concomitant Therapy before the planned first dose of study IMP • Received any investigational IMP 30 days or 5 half-lives (whichever is longer) before the			

Important exclusion criteria	Reason for Exclusion	Is it considered to be included as missing information?	Rationale (if not include as missing information) or reason for exclusion
signing the consent or is currently enrolled in an investigational study			

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 or uncommon 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 6 Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients	Not included in the clinical development program

[redacted]

Type of special population	Exposure
• Patients with a disease severity different from inclusion criteria in clinical trials	
Population with relevant different ethnic origin	Not included in the clinical development program
Subpopulations carrying relevant genetic polymorphisms	No specific exclusions
Other	Not applicable

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure:

Not applicable as product is not yet approved.

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

SVI.1 Potential for misuse for illegal purposes

No evidence to suggest a potential for drug abuse or misuse has been observed.

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

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

- Ear infection, Reversible, mild to moderate, frequency: uncommon (≥ 1/1000 to < 1/100). This is listed event in Summary of Product Characteristic (SmPC) section 4.8.
- Lichenoid drug emptions, Reversible, mild to moderate, frequency: uncommon (≥ 1/1000 to < 1/100). This is a listed event in SmPC section 4.8.

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

[redacted]

- Diverticulitis, Cellulitis. Frequency: uncommon (≥ 1/1000 to < 1/100). These are listed event in SmPC section 4.8.
- Hypersensitivity vasculitis, Frequency: very rare (< 1/10,000). This is listed event in SmPC section 4.8.

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):

- None

Known risks that do not impact the risk-benefit profile:

- None

Other reasons for considering the risks not important:

- None

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

The information presented in Table 7 includes identified and potential risks with Denosumab. The table contains information on identified and potential risks based on the data presented in the SmPC for Denosumab, other biosimilars approved in the EU, and literature articles.

Table 7 Risks considered important for inclusion in the list of safety concerns in the RMP

Risks considered important for inclusion in the list of safety concerns in the RMP	**Risk-benefit impact**
Important Identified Risks	
Hypocalcemia	Clinical monitoring of calcium levels is recommended before each dose and, in patients predisposed to hypocalcaemia within two weeks after the initial dose. If any patient presents with suspected symptoms of hypocalcaemia during treatment (see section 4.8 for

Risks considered important for inclusion in the list of safety concerns in the RMP	**Risk-benefit impact**
	symptoms) calcium levels should be measured. Patients should be encouraged to report symptoms indicative of hypocalcaemia. In the post-marketing setting, severe symptomatic hypocalcaemia (including fatal cases) has been reported, with most cases occurring in the first weeks of initiating therapy, but it can occur later.
Skin infection leading to hospitalization	Patients receiving denosumab may develop skin infections (predominantly cellulitis) leading to hospitalisation. Patients should be advised to seek prompt medical attention if they develop signs or symptoms of cellulitis.
Osteonecrosis of the jaw	Osteonecrosis of jaw has been reported rarely in patients receiving denosumab. A dental examination with preventive dentistry and an individual benefit-risk assessment is recommended prior to treatment with denosumab. All patients should be encouraged to maintain good oral hygiene, receive routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain or swelling, or non-healing of sores or discharge during treatment with denosumab. While on treatment, invasive dental procedures should be performed only after careful consideration and be avoided in close proximity to denosumab administration.
Hypersensitivity reactions	In the post-marketing setting, rare events of drug-related hypersensitivity, including rash, urticaria, facial swelling, erythema, and anaphylactic reactions have been reported in patients receiving denosumab.

Risks considered important for inclusion in the list of safety concerns in the RMP	**Risk-benefit impact**
Atypical femoral fracture	Atypical femoral fractures may occur with little or no trauma in the subtrochanteric and diaphyseal regions of the femur. The event isreported rarely in patients treated with denosumab and the risk increased with longer duration of treatment. Events have occurred during treatment and up to 9 months after treatment was discontinued. During denosumab treatment, patients should be advised to report new or unusual thigh, hip, or groin pain. Patients presenting with such symptoms should be evaluated for an incomplete femoral fracture.
Hypercalcemia in pediatric patients receiving denosumab and after treatment discontinuation	Clinically significant hypercalcaemia after treatment discontinuation has been reported in the post-marketing setting in paediatric patients.
Important Potential Risks	
Fracture healing complications	Because denosumab directly suppresses bone resorption and (indirectly) bone formation, it has the theoretical potential to delay fracture healing. This risk has not been substantiated; however, the effects of denosumab on osteoclasts are fully reversible.
Infection	In the post-marketing setting, infections such as upper respiratory tract infections, ear infection or urinary tract infection have been reported in patients receiving denosumab.
Cardiovascular events	Cardiovascular events have not been reported in pre-

Risks considered important for inclusion in the list of safety concerns in the RMP	**Risk-benefit impact**
	clinical or clinical trials with denosumab. Cardiovascular events were identified through post-marketing data of denosumab. Low calcium in the blood may also lead to a change in heart rhythm called QT prolongation, which is seen by electrocardiogram.
Malignancy	Malignancy in giant cell tumour of bone (GCTB) or progression to metastatic disease is an infrequent event and a known risk in patients with GCTB. Patients should be monitored for radiological signs of malignancy, new radiolucency or osteolysis. Available clinical data does not suggest an increased risk of malignancy in GCTB patients treated with denosumab.
Missing Information	
None	

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

Table 8 Details of important identified risks

Important identified risk: Hypocalcemia	
MedDRA terms (Preferred Terms)	Hypocalcemia

[redacted]

Important identified risk: Hypocalcemia	
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 phase 3, randomized, double-blind, placebo- or active-controlled studies.[3]
Characterisation of the risk	In-line with Prolia RMP, risk has been characterized as follows: Frequency: In the pooled pivotal studies for postmenopausal osteoporosis (PMO) and hormone ablation therapy (HALT) subject incidence of hypocalcemia adverse events was < 0.1 % in denosumab-treated subjects and 0.1% in placebo-treated subjects. The incidence of hypocalcemia adverse events was lower in denosumab-treated subjects than in placebo-treated subjects; thus, 95% Cls (Confidence Intervals) were not calculated. In the 24-month final analysis of the glucocorticoid-induced osteoporosis (GIOP) study, subject incidence of hypocalcemia adverse events was 0.3% in the denosumab group; there were no adverse events of hypocalcemia in the risedronate group thus, 95% Cls were not calculated. Severity: While most hypocalcemia events are mild to moderate in severity, severe events have occurred. Reversibility: Hypocalcemia is reversible when treated with oral calcium and vitamin D supplementation. In severe cases, IV calcium supplementation may be required.

Important identified risk: Hypocalcemia	
	Long-term outcomes: No long-term complications are anticipated for properly treated hypocalcemia. Impact on quality of life: For severe symptomatic hypocalcemia, patients may be hospitalized for treatment. Generally, patients recover when their hypocalcemia is treated.[3]
Risk factors and risk groups	Risk factors include severe renal impairment and hyperphosphatemia. Other risks factors may include a history of hypoparathyroidism, PTH resistance, vitamin D deficiency or resistance, thyroid surgery, parathyroid surgery, malabsorption syndromes, excision of small intestine, severe renal impairment (CrCL < 30 ml/min), dialysis, and some medications.[3]
Preventability	Pre-existing hypocalcemia should be corrected by adequate intake of calcium and vitamin D before initiating therapy, and supplementation with calcium and vitamin D is important during therapy in all patients receiving denosumab. Clinical monitoring of calcium levels is recommended during treatment, especially in those with renal impairment.[3]
Impact on the risk-benefit balance of the product	The risk of hypocalcemia has been considered in the product benefit-risk assessment. Considering the product labeling addressing this risk, the overall benefit-risk balance is considered to be positive.[3]
Public health impact	Significant public health impact is not expected as this risk is preventable and treatable with the appropriate risk mitigating measures communicated clearly in the SmPC.[1]

Important identified risk: Skin Infection Leading to Hospitalisation	
MedDRA terms (Preferred Terms)	Skin Infections
Potential mechanisms	Keratinocytes can express RANK ligand (RANKL) and blocking RANKL in mice decreased the number of regulatory T-cells in skin, leading to an increased inflammatory response.[3]
Evidence source(s) and strength of evidence	This risk was identified in phase 3, randomized, double-blind, placebo- or active-controlled studies.[3]
Characterisation of the risk	In-line with Prolia RMP, risk has been characterized as follows: Frequency: In pooled PMO/HAL T pivotal studies, subject incidence of skin infection was 1.4% with denosumab and 1.3% with placebo; the hazard ratio (HR) was 1.09 (95% Cl: 0. 78, 1.53). Subject incidence of serious adverse events of skin infection was 0.4% with denosumab and 0.2% with placebo (HR [95% Cl]= 2.55 [1.13, 5.76]). In the 24-month final analysis of the GIOP study, subject incidence of adverse events of skin infection was 1.8% with denosumab and 0.5% with risedronate; the HR was 3.62 (95% Cl= 0.75, 17.42). Subject incidence of serious adverse events of skin infection was 0.5% in both the denosumab and risedronate groups (HR [95% Cl] = 1.03 [0.15, 7.34]). Severity: Serious adverse events of skin infection were mostly severe in intensity. Reversibility: These events typically resolved with administration of antibiotics.

Important identified risk: Skin Infection Leading to Hospitalisation	
	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.[3]
Risk factors and risk groups	Risk factors for infection in general include increasing age, immunosuppression associated with cancer, diabetes, HIV/acquired immune deficiency syndrome (AIDS), immunosuppressant drugs (eg, corticosteroids, arthritis medications, and chemotherapy drugs), substance abuse, and malnutrition. Risk factors for skin infection in older patients include skin wounds, peripheral vascular disease, eczema/dermatitis, and venous stasis disorders.[3]
Preventability	No preventive measures are known.
Impact on the risk-benefit balance of the product	The risk of skin infection leading to hospitalisation has been considered in the product benefit-risk assessment. In light of the product labeling addressing this risk, the overall benefit-risk balance is considered to be positive. [3]
Public health impact	Since frequency of skin infection leading to hospitalisation is relatively low, absolute difference between denosumab and placebo groups is relatively small, and the adverse events can be effectively treated by antibiotics, the negative impact to public health is relatively small. [3]

Important identified risk: Osteonecrosis of the Jaw	
MedDRA terms (Preferred Terms)	Osteonecrosis of the Jaw.
Potential mechanisms	Osteonecrosis of the jaw (ONJ) appears to be multifactorial and multiple hypotheses have been postulated and have included factors such as inhibition of bone remodeling, infection and inflammation, inhibition of angiogenesis, soft tissue toxicity, altered immunity and genetic predisposition.[3]
Evidence source(s) and strength of evidence	This risk was identified in open-label long-term extensions to phase 3, randomized, double-blind, placebo-controlled studies.[3]
Characterisation of the risk	In-line with Prolia RMP, risk has been characterized as follows: Frequency: No cases of ONJ have been reported in placebo-controlled studies (although cases were reported in open-label extensions to the pivotal PMO study and a HALT study); thus, 95% Cls were not calculated. No cases of ONJ were reported in the GIOP study. Overall, across the Amgen-sponsored clinical development program for Prolia, positively adjudicated ONJ cases have been reported rarely (18 ONJ cases in 23552 subjects, 0.076%) in subjects cumulatively exposed to denosumab (60 mg) clinical studies. Severity: Most events leading to adjudication as ONJ were assessed as moderate in severity. Mild and severe events were also reported. Reversibility:

Important identified risk: Osteonecrosis of the Jaw	
	In general, ONJ events are clinically reversible with supportive care, antibiotics; however, surgical treatment may be required. <u>Long-term outcomes:</u> No data on long-term outcomes are available. <u>Impact on quality of life:</u> Discomfort associated with ONJ lesions and/or with more extensive treatments may impact patient wellbeing via decreased oral intake (eg, decreased hydration and decreased nutritional intake).[3]
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.[3]
Preventability	A dental examination with appropriate preventive dentistry is recommended prior to treatment with Denosumab, especially in patients with risk factors. While on treatment, patients should avoid invasive dental procedures where possible. Patients who are suspected of having or who develop ONJ while on Denosumab should receive care by a dentist or an oral surgeon. In patients who develop ONJ during treatment with Denosumab, a temporary interruption of treatment

Important identified risk: Osteonecrosis of the Jaw	
	should be considered based on individual risk/benefit assessment until the condition resolves.[3]
Impact on the risk-benefit balance of the product	The risk of osteonecrosis of the jaw has been considered in the product benefit-risk assessment. In light of the product labeling and additional risk minimization activities addressing this risk, the overall benefit-risk balance is considered to be positive.[3]
Public health impact	Significant public health impact is not expected with Denosumab, as the event is rare and the actions taken to minimize the likelihood of developing ONJ are described in the prescribing information.[3]

Important identified risk: Hypersensitivity Reactions	
MedDRA terms (Preferred Terms)	Hypersensitivity
Potential mechanisms	Two types of allergic reactions, immunoglobulin E (lgE)- and non-lgE-mediated, appear to be related to monoclonal antibody administration. The lgE-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-lgE reactions is unclear.[3]
Evidence source(s) and strength of evidence	This risk was identified in the postmarketing setting based on a clinically plausible association between administration of denosumab and hypersensitivity reactions.[3]
Characterisation of the risk	In-line with Prolia RMP, risk has been characterized as follows: Frequency:

Important identified risk: Hypersensitivity Reactions	
	In the pooled PMO/HAL T pivotal studies, subject incidence of hypersensitivity and drug hypersensitivity was 1.0% in denosumab-treated subjects and 0.8% in placebo-treated subjects; HR= 1.26 (95% 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 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]). 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.[3]
Risk factors and risk groups	Known hypersensitivity to denosumab and any of its excipients.[3]

Important identified risk: Hypersensitivity Reactions	
Preventability	No data are available on potential measures to prevent hypersensitivity reactions to denosumab. The appropriate contraindication information on hypersensitivity to denosumab and any of its excipients is included in the SmPC.[3]
Impact on the risk-benefit balance of the product	The risk of hypersensitivity reactions has been considered in the product benefit-risk assessment. In light of the product labeling addressing this risk, the overall benefit-risk balance is considered to be positive.[3]
Public health impact	No significant impact on individual patients is expected.

Important potential risk: Atypical Femoral Fracture (AFF)	
MedDRA terms (Preferred Terms)	Atypical femur fracture, Femur 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, mineralization, remodeling, vascularity, and angiogenesis lend biologic plausibility to a potential association between these effects and AFF.[3]
Evidence source(s) and strength of evidence	This risk was identified in an open-label long-term extension to a phase 3, randomized, double-blind, active-controlled study.[3]

[redacted]

Important potential risk: Atypical Femoral Fracture (AFF)	
Characterisation of the risk	In-line with Prolia RMP, risk has been characterized as follows: Frequency: No cases of confirmed AFF have been reported in placebo-controlled studies; thus, 95% Cls were not calculated. In the GIOP study, subject incidence of confirmed AFF was 0.3% (1 event) in the denosumab group; there were no adverse events of AFF in the risedronate group thus, 95% Cls were not calculated. Overall, as of 26 September 2016, adjudicated-positive cases of AFF have been reported rarely (5 of 23 280 subjects, 0.021%) in subjects exposed to denosumab (60 mg) in clinical studies. Severity: Atypical femoral fracture is a medically important adverse event that generally requires significant medical interventions such as surgery and ongoing monitoring to mitigate risk for and severity of contralateral fractures. The few events from 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:

[redacted]

Important potential risk: Atypical Femoral Fracture (AFF)	
	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.[3]
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. Atypical femoral fractures have also been reported in patients with certain comorbid conditions (eg, vitamin D deficiency, RA, hypophosphatasia) and with use of bisphosphonates, glucocorticoids, and proton pump inhibitors. [3]
Preventability	No data are currently available on potential measures to prevent AFF. Patients using long-term antiresorptives may experience pain over the femur, which requires radiological examination if atypical fracture is suspected.[3]
Impact on the risk-benefit balance of the product	The risk of atypical femoral fracture has been considered in the product benefit-risk assessment. In light of the product labeling addressing this risk, the overall benefit-risk balance is considered to be positive.[3]
Public health impact	Not expected to have a significant public health impact

Important identified risk: Hypercalcemia in Pediatric Patients Receiving Denosumab and After Treatment Discontinuation	
MedDRA terms (Preferred Terms)	Hypercalcemia
Potential mechanisms	The exact mechanism of hypercalcemia occurring in pediatric patients both during the dosing interval and

[redacted]

Important identified risk: Hypercalcemia in Pediatric Patients Receiving Denosumab and After Treatment Discontinuation	
	following discontinuation is not certain but may be a consequence of the following, alone, or in combination: • Hypercalcemia may result from rapid resorption of retained primary spongiosa in a skeleton with active endochondral ossification. The rate of endochondral ossification and duration of exposure to denosumab would determine the amount of accumulated primary spongiosa that could influence the magnitude of resorptive response (mechanostat-driven) and release of calcium from resorbing bone matrix via an autocrine/paracrine mechanism. • The magnitude of the resorptive response following treatment and withdrawal in the immature skeleton could be dictated by the normal high rate of bone turnover in individuals with growing skeletons. • The response of the osteoclast lineage to loss of inhibition of osteoclastogenesis may be intrinsically more robust in individuals with growing skeletons. The increased skeletal metabolism related to bone modeling and growth in children is therefore likely to impact the frequency of hypercalcemia occurring both between the dosing interval and following discontinuation.[3]
Evidence source(s) and strength of evidence	Data to evaluate safety concern were derived from Prolia clinical trials in pediatric subjects with 01, XGEVA clinical studies, and postmarketing adverse event reporting involving pediatric patients receiving denosumab at unapproved doses and/or unapproved indications for use.[3]

[redacted]

Important identified risk: Hypercalcemia in Pediatric Patients Receiving Denosumab and After Treatment Discontinuation	
Characterisation of the risk	In-line with Prolia RMP, risk has been characterized as follows: Frequency: In the completed pediatric OI Study 20130173 during the Q6M dosing regimen, hypercalcemia (Amgen Medical Dictionary for Regulatory Activities [MedDRA] Query [Narrow Search; AMQN]) was reported for 29 subjects (19.0%). All these events were nonserious. During the Q3M dosing regimen and following denosumab discontinuation, hypercalcemia (AMQN) was reported for 22 subjects (36.7%). Serious adverse events of hypercalcemia were reported for 8 subjects (13.3%). Severity: Most subjects in the pediatric OI Study 20130173 receiving the Q3M dosing regimen who had hypercalcemia events experienced mild events. Grade~ 3 hypercalcemia was reported for 10 subjects (16.7%). Grade 4 (life-threatening) hypercalcemia was reported for 4 subjects (6.7%). Reversibility: Hypercalcemia is reversible when treated. In severe cases, use of rescue medications may be required. Long-term outcomes: No long-term adverse effects are anticipated for properly treated hypercalcemia. Impact on quality of life:

Important identified risk: Hypercalcemia in Pediatric Patients Receiving Denosumab and After Treatment Discontinuation	
	Pediatric patients may present with severe hypercalcemia requiring hospitalization. Generally, patients recover when the hypercalcemia is treated.[3]
Risk factors and risk groups	Pediatric patients with growing skeletons and high bone turnover disease states.[3]
Preventability	Denosumab is not indicated in pediatric patients (age< 18 years) and should not be used in pediatric patients.[3]
Impact on the risk-benefit balance of the product	The benefit-risk profile of Denosumab is not favorable in the pediatric patient population.[3]
Public health impact	Significant public health impact is not expected as this risk is preventable with the appropriate risk mitigating measures communicated clearly in the SmPC.[1]

Important Potential risk: Fracture Healing Complications	
MedDRA terms (Preferred Terms)	Fracture malunion (PT), Malunion and nonunion of fracture (LLT)
Potential mechanisms	Because denosumab directly suppresses bone resorption and (indirectly) bone formation, it has the theoretical potential to delay fracture healing.[3]
Evidence source(s) and strength of evidence	This is a theoretical risk based on the mechanism of action.[3]
Characterisation of the risk	In-line with Prolia RMP, risk has been characterized as follows: Frequency: Of the subjects who had nonvertebral fractures in the large pivotal PMO study, fracture healing complications (delayed healing or nonunion) were

[redacted]

Important Potential risk: Fracture Healing Complications	
	reported in 2 of 386 subjects in the denosumab group (0.5%) and 5 of 465 subjects (1.1 %) in the placebo group. Of the subjects who had nonvertebral fractures in the pivotal study for HALT-breast cancer, fracture healing complications were reported in 0 of 8 subjects in the denosumab group and 1 of 8 subjects (12.5%) in the placebo group. Because of the low incidence of fracture healing complications, 95% Cls were not calculated. No fracture healing complications were reported in the MOP study. No fracture healing complications were reported in the GIOP study. Severity: This risk has not been substantiated; however, impaired fracture healing could have a significant impact on patient wellbeing. Reversibility: This risk has not been substantiated; however, the effects of denosumab on osteoclasts are fully reversible. Long-term outcomes: This risk has not been substantiated; however, no long-term impact would be anticipated based on reversibility. Impact on quality of life: Fracture healing complications can cause short-term or long-term disability. Surgery may be required.[3]
Risk factors and risk groups	General risk factors for fracture healing complications are thought to include older age, diabetes, use of

Important Potential risk: Fracture Healing Complications	
	medications such as non-steroidal anti-inflammatory drugs and corticosteroids, smoking, excessive alcohol use, and poor nutrition.[3]
Preventability	No preventive measures are known
Impact on the risk-benefit balance of the product	The potential risk of fracture healing complications has been considered in overall assessment supporting a positive benefit-risk profile.[3]
Public health impact	No significant impact on public health is anticipated

Important potential risk: Infection	
MedDRA terms (Preferred Terms)	Infections
Potential mechanisms	RANK ligand is expressed on activated T and B cells and in the lymph nodes and some reports have described immune modulatory effects of RANKL inhibition. However, no clinically relevant effect of denosumab treatment was observed on peripheral blood immune cell subset profiles in studies in healthy elderly men, postmenopausal women, and postmenopausal women with low BMD.[3]
Evidence source(s) and strength of evidence	This is considered a potential risk based on theoretical concerns which has not been substantiated in the extensive clinical study program or in the postmarketing experience.[3]
Characterisation of the risk	<u>In-line with Prolia RMP, risk has been characterized as follows:</u> <u>Frequency:</u> In the 24-month final analysis of the GIOP study, subject incidence of infections was 36.3% with denosumab and 36.4% with risedronate; HR= 1.06

[redacted]

Important potential risk: Infection	
	(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]). 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.[3]
Risk factors and risk groups	Risk factors for infection in general include increasing age, immunosuppression associated with cancer, diabetes, HIV/AIDS, immunosuppressant drugs (eg, corticosteroids, arthritis medications, and chemotherapy drugs), substance abuse, and malnutrition.[3]
Preventability	No preventive measures are known.
Impact on the risk-benefit balance of the product	The potential risk of infection has been considered in the overall assessment which supports a positive benefit-risk profile in the indicated populations.[3]

Important potential risk: Infection	
Public health impact	No significant public health impact is expected for this unsubstantiated risk as effective treatments are available.[3]

Important potential risk: Cardiovascular Events	
MedDRA terms (Preferred Terms)	Cardiac disorders (SOC), Vascular disorders (SOC)
Potential mechanisms	Elevated levels of OPG have been associated with coronary artery disease in cross-sectional studies but this association has been contradicted by preclinical and epidemiological studies demonstrating that the lack of OPG or unopposed RANKL is associated with cardiac calcification. Because of these conflicting results and because denosumab inhibits RAN KL, a theoretical concern for denosumab to affect progression of atherosclerosis exists.[3]
Evidence source(s) and strength of evidence	This is a theoretical risk based on epidemiological data demonstrating elevated OPG in patients with cardiovascular disease.[3]
Characterisation of the risk	In-line with Prolia RMP, risk has been characterized as follows: Frequency In a pooled analysis of the large pivotal PMO study (20030216) and the pivotal HALT-prostate study, the overall subject incidence of adjudicated-positive serious cardiovascular events was 5.8% with denosumab and 5.6% with placebo (HR [95% Cl] = 1.00 [0.85, 1.19]). During the placebo-controlled phase of the pivotal study for MOP, adverse events in the cardiac disorders

Important potential risk: Cardiovascular Events	
	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 Ml-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). <u>Severity:</u> This risk has not been substantiated; however, cardiovascular events may be severe/life-threatening. <u>Reversibility:</u>

Important potential risk: Cardiovascular Events	
	This risk has not been substantiated; however, effects of denosumab to block RANKL are fully 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.[3]
Risk factors and risk groups	The denosumab development program comprises studies of older subject populations (eg, osteoporosis, cancer) that are likely to have a higher incidence of pre-existing cardiovascular conditions and, thus, a higher incidence of cardiovascular toxicities than that of the general population. 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.[3]
Preventability	No preventive measures are known.[3]
Impact on the risk-benefit balance of the product	The potential risk of cardiovascular events has been considered in overall assessment supporting a positive benefit-risk profile[3]
Public health impact	Significant public health impact of Denosumab on cardiovascular disease severity or incidence is not anticipated.[3]

Important potential risk: Malignancy	
MedDRA terms	Malignancies (SMQ)
Potential mechanisms	RANK ligand is expressed on activated T and B cells and in the lymph nodes and some reports have described immune modulatory effects of RANKL inhibition; however, in vitro studies of RANK and RANKL activity on a wide range of human tumor types provide no evidence for carcinogenic risk associated with RANKL inhibition.[3]
Evidence source(s) and strength of evidence	This is considered a potential risk based on theoretical concerns and has not been substantiated in the extensive clinical study program or in the postmarketing experience.[3]
Characterisation of the risk	In-line with Prolia RMP, risk has been characterized as follows: Frequency: In a large pivotal PMO study (20030216), 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 MOP study, 4 subjects in the denosumab group (3.3%) and no subject in the placebo group reported events of malignancy. The events were prostate cancer in 3 subjects and basal cell carcinoma in 1 subject. Two prostate cancer cases were likely present at baseline based on past medical history. In the

Important potential risk: Malignancy	
	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. 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 eg, surgery, radiation, and/or chemotherapy.[3]
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.[3]

[redacted]

Important potential risk: Malignancy	
Preventability	No preventive measures are known.
Impact on the risk-benefit balance of the product	The potential risk of malignancy has been considered in the product benefit-risk assessment which supports a positive benefit-risk profile in the indicated populations.[3]
Public health impact	Significant public health impact is not anticipated

SVII.3.2. Presentation of the missing information

Not Applicable

Part II: Module SVIII - Summary of the safety concerns

Table 9 Summary of safety concerns

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

[redacted]

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

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities including collection and reporting of adverse reactions and signal detection as stated in pharmacovigilance system master file are sufficient for the safety concerns mentioned in module SVIII.

As part of the routine pharmacovigilance procedures for biologics, information about trade name and batch numbers will be required as part of case validation. As per Accord procedural documents, Accord shall record trade names and batch numbers of any adverse events reported in association with the use of any Osvyrti (Denosumab).

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaire for safety concerns listed below:

- Hypocalcemia
- Infection
- Osteonecrosis of the jaw
- Postmarketing reports of potential atypical fracture
- Fracture healing
- Malignancy
- Hypersensitivity

Purpose: Follow-up questionnaire wise purpose is described as follows:

- To monitor the nature of hypocalcemia in patients treated with denosumab in the postmarketing environment.
- To monitor the nature of skin infections leading to hospitalisation and infections of any type reported in patients treated with denosumab in the postmarketing environment.
- To monitor the nature of ONJ in patients treated with denosumab in the postmarketing environment.

- To monitor the nature of AFF reported in patients treated with denosumab in the postmarketing environment.
- To monitor the nature of fracture healing complications reported in patients treated with denosumab in the postmarketing environment.
- To monitor the nature of malignancy adverse events reported in patients treated with denosumab in the postmarketing environment.
- To monitor the nature of hypersensitivity reported in patients treated with denosumab in the postmarketing environment.

Targeted follow-up questionnaires and data collection forms are appended in Annex 4: Specific adverse drug reaction follow-up forms of this RMP.

III.2 Additional pharmacovigilance activities

Not applicable

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable

Part IV: Plans for post-authorisation efficacy studies

Not applicable

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

V.1. Routine Risk Minimisation Measures

The following table presents a summary of the safety concerns and the routine risk minimisation activities.

Table 10 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important Identified Risks	
Hypocalcemia	*Routine risk communication*: • SmPC Section 4.2, 4.3, 4.4, and 4.8 • Package leaflet (PL) Section 2 and 4 *Routine risk minimisation activities recommending specific clinical measures to address the risk*: • Recommendation for correction of hypocalcemia prior to initiating treatment with Osvyrti and clinical monitoring of calcium levels during treatment with Osvyrti is included in SmPC Section 4.4. *Other routine risk minimisation measure beyond the Product Information:* • The prescription only status of the product.
Skin infection leading to hospitalisation	*Routine risk communication:* • SmPC Section 4.4 and 4.8 • PL Section 2 and 4 *Routine risk minimization activities recommending specific clinical measures to address the risk:* • None *Other routine risk minimisation measure beyond the Product Information:*

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

	Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendation for reporting new or unusual thigh, hip, or groin pain is included in SmPC Section 4.4. *Other routine risk minimisation measure beyond the Product Information:* • The prescription only status of the product.
Hypercalcemia in pediatric patients receiving denosumab and after treatment discontinuation	*Routine risk communication:* • SmPC Section 4.2, 4.4, and 4.8 • PL Section 2 *Routine risk minimization activities recommending specific clinical measures to address the risk:* • None *Other routine risk minimisation measure beyond the Product Information:* • The prescription only status of the product.
Important Potential Risks	
Fracture healing complications	*Routine risk communication:* • SmPC Section 5.3 *Routine risk minimization activities recommending specific clinical measures to address the risk:* • None *Other routine risk minimisation measure beyond the Product Information:* • The prescription only status of the product.

[redacted]

Infection	*Routine risk communication:* • SmPC Section 4.8 • PL Section 4 *Routine risk minimization activities recommending specific clinical measures to address the risk:* • None *Other routine risk minimisation measure beyond the Product Information:* • The prescription only status of the product.
Cardiovascular events	*Routine risk communication:* • None *Routine risk minimization activities recommending specific clinical measures to address the risk:* • None *Other routine risk minimisation measure beyond the Product Information:* • The prescription only status of the product.
Malignancy	*Routine risk communication:* • None *Routine risk minimization activities recommending specific clinical measures to address the risk:* • None *Other routine risk minimisation measure beyond the Product Information:* • The prescription only status of the product.
Missing Information	
None	

V.2. Additional Risk Minimisation Measures

Additional Risk Minimisation Measure has been proposed for following risk as per reference medicinal product Prolia® (Denosumab):

- Osteonecrosis of the jaw

Proposed additional risk minimisation measures are listed below and are summarised in Annex 6.

Additional risk minimisation measures

Objectives:

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

Rationale for the additional risk minimization activity:

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

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

Target audience and planned distribution path:

- Target audience will be the patients
- The patient reminder card will be distributed to prescribers with instruction to provide it to patients

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

Routine pharmacovigilance activities involving analysis of ADR reports to assess compliance with SmPC recommendations will allow assessing and judging the success of the risk minimisation measures. Effectiveness of this measure will be analysed by MAH as per the requirements for submission of periodic safety update reports (PSUR) for this medicinal product are set out in the list of European Union Reference Dates (EURD list) provided as per Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the

[redacted]

European Medicines Agency's web-portal and also will be evaluated in details in periodic signal management activity.

V.3 Summary of risk minimisation measures

Table 11 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks		
Hypocalcemia	Routine risk minimization measures: • SmPC Section 4.2, 4.3, 4.4 and 4.8 • PL Section 2 and 4 • Recommendation for correction of hypocalcemia prior to initiating treatment with Osvyrti and clinical monitoring of calcium levels during treatment with Osvyrti is included in SmPC Section 4.4. • The prescription only status of the product. Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire for hypocalcemia Additional pharmacovigilance activities: • None
Skin infection leading to hospitalisation	Routine risk minimization measures:	Routine pharmacovigilance activities beyond adverse

	• SmPC Section 4.4 and 4.8 • PL Section 2 and 4 • The prescription only status of the product. <u>Additional risk minimization measures:</u> • None	<u>reactions reporting and signal detection:</u> • Follow-up questionnaire for Infection <u>Additional pharmacovigilance activities:</u> • None
Osteonecrosis of the Jaw	<u>Routine risk minimization measures</u>*:* • SmPC Section 4.8 • PL Section 2 and 4 • Recommendation for oral examination, maintenance of good oral hygiene during treatment, management of patients with unavoidable invasive dental procedures, and temporary interruption of treatment if ONJ occurs is included in SmPC Section 4.4. • The prescription only status of the product. <u>Additional risk minimization measures:</u> • Patient reminder card	<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> • Follow-up questionnaire for Osteonecrosis of the Jaw <u>Additional pharmacovigilance activities:</u> • None

[redacted]

Hypersensitivity reactions	<u>Routine risk minimization measures:</u> • SmPC Section 4.3 and 4.8 • PL Section 4 • The prescription only status of the product. <u>Additional risk minimization measures:</u> • None	<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> • Follow-up questionnaire for Hypersensitivity <u>Additional pharmacovigilance activities:</u> • None
Atypical femoral fracture	<u>Routine risk minimization measures:</u> • SmPC Section 4.4 and 4.8 • PL Section 2 and 4 • Recommendation for reporting new or unusual thigh, hip, orgroin pain is included in SmPC Section 4.4. • The prescription only status of the product. <u>Additional risk minimization measures:</u> • None	<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> • Follow-up questionnaire for Atypical femoral fracture <u>Additional pharmacovigilance activities:</u> • None
Hypercalcemia in pediatric patients receiving denosumab and after treatment discontinuation	<u>Routine risk minimization measures:</u> • SmPC Section 4.2, 4.4, and 4.8 • PL Section 2	<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> • None

[redacted]

	• The prescription only status of the product. Additional risk minimization measures: • None	Additional pharmacovigilance activities: • None
Important Potential Risks		
Fracture healing complications	Routine risk minimization measures: • SmPC Section 5.3 • The prescription only status of the product. Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire for fracture healing complications Additional pharmacovigilance activities: • None
Infection	Routine risk minimization measures: • SmPC Section 4.8 • PL Section 4 • The prescription only status of the product Additional risk minimization measures: • None	*Routine pharmacovigilance* activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire for infection *A*dditional pharmacovigilance activities: • None
Cardiovascular events	Routine risk minimization measures:	Routine pharmacovigilance activities beyond adverse

	• The prescription only status of the product dditional risk minimization measures: • None	reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Malignancy	Routine risk minimization measures: • The prescription only status of the product Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire for malignancy Additional pharmacovigilance activities: • None
Missing Information		
None		

Part VI: Summary of the risk management plan

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

This is a summary of the risk management plan (RMP) for Osvyrti 60 mg solution for injection in pre-filled syringe. The RMP details important risks of Osvyrti 60 mg solution for injection in pre-filled syringe, how these risks can be minimised, and how more information will be obtained about Osvyrti 60 mg solution for injection in pre-filled syringe's risks and uncertainties (missing information).

Osvyrti 60 mg solution for injection in pre-filled syringe's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Osvyrti 60 mg solution for injection in pre-filled syringe should be used.

This summary of the RMP for Osvyrti 60 mg solution for injection in pre-filled syringe 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 Osvyrti 60 mg solution for injection in pre-filled syringe's RMP.

I. The medicine and what it is used for:

Osvyrti 60 mg solution for injection in pre-filled syringe is indicated for:

- Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures. In postmenopausal women denosumab significantly reduces the risk of vertebral, non-vertebral and hip fractures.
- 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, denosumab 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.

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

[redacted]

Further information about the evaluation of Osvyrti 60 mg solution for injection in pre-filled syringe's benefits can be found in Osvyrti 60 mg solution for injection in pre-filled syringe's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <link to the EPAR summary landing page>.

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

Important risks of Osvyrti 60 mg solution for injection in pre-filled syringe, together with measures to minimise such risks and the proposed studies for learning more about Osvyrti 60 mg solution for injection in pre-filled syringe'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 Osvyrti 60 mg solution for injection in pre-filled syringe, 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*.

II.A List of important risks and missing information

Important risks of Osvyrti 60 mg solution for injection in pre-filled syringe 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

[redacted]

of Osvyrti 60 mg solution for injection in pre-filled syringe. 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).

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

II.B Summary of important risks

Important identified risk: Hypocalcemia	
Evidence for linking the risk to the medicine	This risk was identified in phase 3, randomized, double-blind, placebo- or active-controlled studies.[3]
Risk factors and risk groups	Risk factors include severe renal impairment and hyperphosphatemia. Other risks factors may include a history of hypoparathyroidism,

[redacted]

	parathyroid hormone resistance, vitamin D deficiency or resistance, thyroid surgery, parathyroid surgery, malabsorption syndromes, excision of small intestine, severe renal impairment (creatinine clearance< 30 mUmin), dialysis, and some medications.[3]
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.2, 4.3, 4.4 and 4.8 • PL Section 2 and 4 • Recommendation for correction of hypocalcemia prior to initiating treatment with Osvyrti and clinical monitoring of calcium levels during treatment with Osvyrti is included in SmPC Section 4.4. • The prescription only status of the product. Additional risk minimization measures: • None
Important identified risk: Skin infection leading to hospitalization	
Evidence for linking the risk to the medicine	This risk was identified in phase 3, randomized, double-blind, placebo- or active-controlled studies.[3]
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 (eg, corticosteroids, arthritis medications, and chemotherapy drugs), substance abuse, and malnutrition.

	Risk factors for skin infection in older patients include skin wounds, peripheral vascular disease, eczema/dermatitis, and venous stasis disorders.[3]
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 and 4.8 • PL Section 2 and 4 • The prescription only status of the product. Additional risk minimization 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 3, randomized, double-blind, placebo-controlled studies.[3]
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.[3]
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.8 • PL Section 2 and 4

[redacted]

	• Recommendation for oral examination, maintenance of good oral hygiene during treatment, management of patients with unavoidable invasive dental procedures, and temporary interruption of treatment if ONJ occurs is included in SmPC Section 4.4. • The prescription only status of the product. Additional risk minimization measures: • Patient reminder card
Important identified risk: Hypersensitivity reactions	
Evidence for linking the risk to the medicine	This risk was identified in the postmarketing setting based on a clinically plausible association between administration of denosumab and hypersensitivity events.[3]
Risk factors and risk groups	Known hypersensitivity to denosumab and any of its excipients.[3]
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.3 and 4.8 • PL Section 4 • The prescription only status of the product. Additional risk minimization 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 3, randomized, double-blind, active-controlled study.[3]

[redacted]

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 Atypical femoral fractures have also been reported in patients with certain comorbid conditions (eg, vitamin D deficiency, rheumatoid arthritis, hypophosphatasia) and with use of bisphosphonates, glucocorticoids, and proton pump inhibitors.[3]
Risk minimization measures	<u>Routine risk minimization measures:</u> • SmPC Section 4.4 and 4.8 • PL Section 2 and 4 • Recommendation for reporting new or unusual thigh, hip, orgroin pain is included in SmPC Section 4.4. • The prescription only status of the product. <u>Additional risk minimization measures:</u> • None
Important identified risk: Hypercalcemia in pediatric patients receiving denosumab and after treatment discontinuation	
Evidence for linking the risk to the medicine	Data to evaluate safety concerns derived from Prolia clinical trials in pediatric subjects with osteogenesis imperfecta, XGEVA clinical studies and postmarketing adverse event reporting involving pediatric patients receiving denosumab at unapproved doses and/or unapproved indications for use.[3]

[redacted]

Risk factors and risk groups	Pediatric patients with growing skeletons and high bone turnover disease states (such as osteogenesis imperfecta).[3]
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.2, 4.4, and 4.8 • PL Section 2 • The prescription only status of the product. Additional risk minimization 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.[3]
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.[3]
Risk minimization measures	Routine risk minimization measures: • SmPC Section 5.3 • The prescription only status of the product. Additional risk minimization 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 study program or in the postmarketing experience.[3]
Risk factors and risk groups	Risk factors for infection in general include increasing age, immunosuppression associated with cancer, diabetes, HIV/AIDS, immunosuppressant drugs (eg, corticosteroids, arthritis medications, and chemotherapy drugs), substance abuse, and malnutrition.[3]
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.8 • PL Section 4 • The prescription only status of the product Additional risk minimization measures: • None
Important potential risk: Cardiovascular events	
Evidence for linking the risk to the medicine	This is a theoretical risk based on epidemiological data demonstrating elevated osteoprotegerin in patients with cardiovascular disease.[3]
Risk factors and risk groups	The denosumab development program comprises studies of older subject populations (eg, osteoporosis, cancer) that are likely to have a higher incidence of pre-existing cardiovascular conditions and, thus,

[redacted]

	a higher incidence of cardiovascular toxicities than that of the general population. 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.[3]
Risk minimization measures	<u>Routine risk minimization measures:</u> • The prescription only status of the product <u>Additional risk minimization measures</u>: • None
Important potential risk: Malignancy	
Evidence for linking the risk to the medicine	This is considered a potential risk based on theoretical concerns and has not been substantiated in the extensive clinical study program or in the postmarketing experience.[3]
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.[3]

Risk minimization measures	Routine risk minimization measures: • The prescription only status of the product Additional risk minimization 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 Osvyrti 60 mg solution for injection in pre-filled syringe.

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

There are no studies required for Osvyrti 60 mg solution for injection in pre-filled syringe.

[redacted]

Annex 4: Specific adverse drug reaction follow-up forms

The MAH has proposed targeted follow up questionnaires for following safety concerns concerning the use of Osvyrti and they are appended below:

- Hypocalcemia
- Infection
- Osteonecrosis of the jaw
- Postmarketing reports of potential atypical fracture.
- Fracture healing.
- Malignancy
- Hypersensitivity

Targeted follow up questionnaire for Hypocalcaemia

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

Patient Identifier: _____ Patient Initials: _____ Date of this report: ___/___/_____

Gender: ☐ Male ☐ Female Weight: _____lb _____kg Age at the time of event: ___/___/_____

Date of event onset: ___/___/_____ Event reported term: _____

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

Denosumab Indication

☐ Postmenopausal osteoporosis

☐ Bone loss from hormone ablation therapy

Please specify diagnosis _____

_____

☐ Advanced cancer with bone metastasis

Please specify cancer_____

☐ Others

Please specify_____

_____

☐ Don't know

Denosumab Dose

☐ 60 mg SC every 6 months

☐ 120 mg SC every 4 weeks

☐ Other Please specify_____

☐ Don't know.

Denosumab Exposure

Denosumab first administered (date)_____

Last Denosumab dose before event (date)_____

☐Doses of denosumab skipped ☐Yes ☐No ☐ Unk

If yes, please specify_____

☐Doses of denosumab give after event began

☐Yes ☐ No ☐ Unknown

If yes, date of first dose following start of event_____

ADVERSE EVENT: PATIENT'S SYMPTOMS/SIGNS

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

☐ Convulsions ☐ Muscle Cramping

☐ Muscle twitching ☐ Paraesthesia

☐ Syncope ☐ Tetany

☐ None ☐ Other _____

DIAGNOSI S(Check all that apply)

- Serum calcium at time of event _____ mg/dL ☐Unknown

Please provide serum albumin result_____

- Serum albumin at the time of event < 4.0 g/dL ☐ Yes ☐ No ☐ Unknown

If yes, what were the ion1zed calcium levels? _____nnol/dL

- Serum creatinine at time of event was > 2.0 X times upper limit of normal?

  ☐ Yes ☐ No ☐ Unknown

  Please provide results _____

- Hypocalcaemia induced EKG changes (QT prolongation)? ☐ Yes ☐No ☐ Unknown

[redacted]

TREATMENT

Treated only as an outpatient?	☐ Yes	☐ No		
If yes, route of calcium replacement	☐ IV	☐ Oral	☐ Unknown	
Treated in ER?	☐ Yes	☐No		
If yes, route of calcium replacement?	☐ IV	☐ Oral	☐ Unknown	
Treatment included general hospital admission for calcium replacement?				
	☐ Yes	☐ No	☐ Unknown.	
If yes, route of calcium replacement:	☐ IV	☐ Oral	☐ Unknown	
Treatment included ICU admission	☐ Yes	☐ No	☐ Unknown.	
If yes, route of calcium replacement:	☐ IV	☐ Oral	☐ Unknown	
Overall length of hospital stay:	☐ ≤ 01 day	☐ >1 day	☐ ≤ 7 days	☐ ≥ 7 Days
Anti-arrhythmic medications?	☐ Yes	☐ No	☐ Unknown	

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

Anti-arrhythmic medications? _____

Other treatment? ☐ Yes ☐ No ☐ Unknown

If yes, please specify? _____

RISK FACTORS (Check all that apply)

Medical History Risk Factors

Does the patient have any of the following risk factors? ☐ Yes ☐ No If yes, please provide dates and details:

☐Acute Pancreatitis	☐History of chronic renal disease	_____
☐History of parathyroid disease	☐History of hypoalbuminemia	_____
☐History of malignancy	☐Hypoproteinaemia	_____
☐Hyperphosphatemia	☐Magnesium deficiency	_____
☐Recent Surgery	☐Sepsis	_____

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

Please provide the Vitamin D levels at the time of hypocalcaemia event.

_____

☐ Prior hypocalcaemia event (before denosumab treatment)

Please provide the dates and details of prior hypocalcaemia event.

_____

_____

Medication Risk Factors:

Antineoplastic agent? (Check which apply)

[redacted]

☐ Cisplatin ☐ Cytosine arabinoside ☐ Other ☐ None.

Antimicrobials? (Check which apply)

☐ Pentamidine ☐ Ketoconazole ☐ Other ☐ None.

CONCOMITANT MEDICATION

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

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

Other concomitant medications?

_____

☐ Hypocalcemic event resolved ☐ Yes ☐ No ☐ Unknown

If yes, date (DD/MM/YYYY):_____

REPORTER DETAILS:

Title, Name & Surname	Occupation	Signature	Date
Postal Address: Postcode:	Email:	Tel No.	

[redacted]

Targeted follow-up questionnaire for Infection

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

Patient Identifier: _____ Patient Initials: _____ Date of this report: ___/___/_____

Gender: ☐ Male ☐ Female Weight: _____lb _____kg Age at the time of event: ___/___/_____

Date of event onset: ___/___/_____ Event reported term: _____

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

Denosumab Indication

☐ Postmenopausal osteoporosis

☐ Bone loss from hormone ablation therapy

Please specify diagnosis _____

_____

☐ Advanced cancer with bone metastasis

Please specify cancer_____

☐ Others

Please specify_____

_____

☐ Done know

Denosumab Dose

☐ 60 mg SC every 6 months

☐ 120 mg SC every 4 weeks

☐ Other Please specify_____

☐ Done know.

Denosumab Exposure

Denosumab first administered (date)_____

Last Denosumab dose before event (date)_____

☐Doses of denosumab skipped ☐Yes ☐No ☐ Unk

If yes, please specify_____

☐Doses of denosumab give after event began.

☐Yes ☐ No ☐ Unknown.

If yes, date of first dose following start of event_____

SIGN AND SYMPTOMS (Check all that apply,provide dates of onset, resolution, if available)

☐ Fever _____ ☐ Prolonged fatigue_____ ☐ Cough_____ ☐ Diarrhea_____

☐ Swelling_____ ☐ Pain_____ ☐Discharge_____ ☐ Shortness of breath_____

Location_____Location_____ Location_____ and Description_____

☐ Rash_____☐Chills_____ ☐Night sweats_____☐Other_____

Location_____

☐ Organ system affected.

☐Cardiac ☐Ear/Nose ☐ Throat ☐Gastrointestinal ☐Respiratory

☐ Musculoskeletal (including joints)

☐ Nervous (Cerebrospinal fluid) ☐Skin location ----------

☐ Kidney/genito-urinary ☐ Systemic (bacteraemia and/or sepsis) ☐ Other----------

[redacted]

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

Diagnostic	Results/Units	Reference Range/Units	Date (DD/MM/YYYY)	Report Attached (Y/N)	

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

CHECK WHICH INFECTION APPLIES

☐ Cardiac infections
- ☐ Endocarditis_____
- ☐ Pericarditis (purulent; tuberculous) _____
- ☐ Other, please specify _____

☐ Ear and labyrinth infections
- ☐ Otits media_____
- ☐ Otitis extema_____
- ☐ Other, please specify_____

☐ Gastrointestinal/abdominal infections
- ☐ Colitis_____
- ☐ Diverticulitis_____
- ☐ Appendicitis_____
- ☐ Abdominal sepsis (including peritonitis) _____

- ☐ Hepatic abscess_____
- ☐ Hepatitis B_____
- ☐ Hepatitis C_____
- ☐ Other, please specify_____

☐ Musculoskeletal and connective tissue infections

- ☐ Osteomyelitis _____
- ☐ Septic arthritis _____
- ☐ Other, please specify_____

☐ Nervous system infections

- ☐ Meningitis_____
- ☐ Encephalitis_____
- ☐ Other, please specify_____

☐ Respiratory tract infections

- ☐ Pneumonia_____
- ☐ Pulmonary TB_____
- ☐ Lung abscess _____
- ☐ Legionnella pneumonia_____
- ☐ Mycoplasma pneumonia_____
- ☐ Other, please specify_____

☐ Kidney and genito-urinary tract infections

- ☐ Cystitis_____
- ☐ Pyelonephritis_____
- ☐ Urinary tract infection_____
- ☐ Other, please specify_____

☐ Systemic infections

- ☐ Bacteremia_____
- ☐ Sepsis_____
- ☐ Toxic shock syndrome_____
- ☐ Other, please specify_____

☐ Wound and skin infections.

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

☐ Opportunistic infections

- ☐ Aspergillus (invasive forms only) _____
- ☐ Blastomycosis pulmonary or extra-pulrnonary infections _____
- ☐ Candidiasis systemic _____
- ☐ Coccidioidomycosis secondary/systemic_____
- ☐ Cryptococcal infection pulmonary and non-pulmonary _____
- ☐ Cytomegalovirus — include systemic site _____
- ☐ Herpes simplex (meningitis or encephaltits) _____
- ☐ Herpes zoster (only systemic or disseminated: involving 2 or more dermatomes) _____
- ☐ Histoplasma infections - chronic disseminated or severe acute _____
- ☐ Mucormycosis (=zygomycosis) including infections due to Rhizopus, Mucor and Absidia of lung, genito-urinary tract, kidney, GIT, skin_____
- ☐ Mycobacterium tuberculosis _____
- ☐ Non-tuberculosis mycobacterium _____
- ☐ Nocardia infection - of brain, lungs, kidney, skin_____
- ☐ Paracoccidioides infections of lungs, skin other _____

[redacted]

☐ *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: ☐ No ☐ Yes ☐ Unknown.

If yes, check which apply:

☐ Blood culture_____

☐ Culture positive ☐ No ☐ Yes ☐ Unknown
If yes, which: ☐ Bacterial ☐ Fungal ☐ Viral
☐ Pathogen identified: _____

☐ Urine culture_____

☐ Culture positive ☐ No ☐ Yes ☐ Unknown
If yes, which: ☐ Bacterial ☐ Fungal ☐ Viral
☐ Pathogen identified: _____

☐ Sputum culture_____

☐ Culture positive ☐ No ☐ Yes ☐ Unknown
If yes, which: ☐ Bacterial ☐ Fungal ☐ Viral
☐ Pathogen identified: _____

☐ Synovial culture_____

☐ Culture positive ☐ No ☐ Yes ☐ Unknown
If yes, which: ☐ Bacterial ☐ Fungal ☐ Viral
☐ Pathogen identified: _____

☐ Cerebrospinal fluid culture_____

☐ Culture positive ☐ No ☐ Yes ☐ Unknown
If yes, which: ☐ Bacterial ☐ Fungal ☐ Viral
☐ Pathogen identified: _____

☐ Tissue culture_____

If yes, specify: ☐ Brain ☐ Lung ☐ Liver ☐ Kidney ☐ Skin ☐ Bone ☐ Other
☐ Pathogen identified: _____
☐ Culture positive ☐ No ☐ Yes ☐ Unknown
If yes, which: ☐ Bacterial ☐ Fungal ☐ Viral
☐ Pathogen identified: _____

☐ Catheter Tip/Line_____

☐ Culture positive ☐ No ☐ Yes ☐ Unknown
If yes, which: ☐ Bacterial ☐ Fungal ☐ Viral
☐ Pathogen identified: _____

☐ PPD placement: ☐ No ☐ Yes ☐ Unknown
If yes, PPD positive ☐ No ☐ Yes ☐ Unknown

☐ Parasitic evaluation (ova, etc.) _____

[redacted]

☐ X ray ☐ No ☐ Yes ☐ Unknown _____
☐ MRI ☐ No ☐ Yes ☐ Unknown _____
☐ CT scan ☐ No ☐ Yes ☐ Unknown _____
☐ Bone scan ☐ No ☐ Yes ☐ Unknown _____
☐ Other _____
☐ Rapid test _____
☐ Serum titres _____
☐ Hospital discharge report _____
☐ Other consult report _____
☐ Provide final diagnosis and treatment, if available _____
☐ Outcome and resolution date _____

TREATMENT

☐ ER antibiotics ☐ No ☐ Yes ☐ Unknown.

If yes, Route: ☐ IV ☐ Oral ☐ SC ☐ Both oral and IV

☐ Required hospital admission ☐ Yes ☐ No ☐ Unknown.

☐ ICU admission ☐ Yes ☐ No ☐ Unknown

If yes, reason for ICU admission_____

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

_____

☐ In hospital antibiotics, ☐ No ☐ Yes ☐ Unknown

If yes Route ☐ IV only ☐ Oral only ☐ Both oral and IV

☐ Other in hospital treatment:

☐ Antivirals: ☐ No ☐ Yes ☐ Unknown

If yes Route ☐ IV ☐ Oral

☐ Antifungals: ☐ No ☐ Yes ☐ Unknown

If yes Route ☐ IV ☐ Oral

☐ Surgery ☐ No ☐ Yes ☐ Unknown

☐ Hyperbaric oxygen ☐ No ☐ Yes ☐ Unknown

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

Please specify any post operative completions, 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_____

[redacted]

☐ Chemotherapy_____
☐ Malnutrition/failure to thrive_____
☐ Exposure to infectious agents_____
☐ Personal contact_____ ☐ Body fluids_____
☐ Share personal items (razor, needles, etc) _____
☐ Potentially contaminated food/liquid_____
☐ Exposure to infectious agents (continued) _____
☐ Hospital acquired_____
☐ other_____
☐ Steroid exposure_____
☐ Insect/tick bite _____
☐ Drug or IV drug abuse: Type_____
Amount _____
Frequency_____
☐ Alcohol/tobacco use: Type_____
Amount _____
Frequency_____
☐ Indwelling catheters: _____
☐ Recent skin injury: _____
☐ Recent travel (specify): _____
☐ Exposure to animals/zoonotic diseases (exposure to infected animal): _____
☐ Unprotected sex: _____
☐ Immobility: _____
☐ Indwelling catheters_____
☐ Nursing home resident_____
☐ Occupational exposure: _____
☐ Ostomy: _____
☐ Post influenza: _____
☐ Surgery < 30 days: _____
☐ TB exposure: _____
☐ Other history/risk factors: _____

REPORTER DETAILS:

Name	Signature	Date
Address: City: Country: State/Province: Postal code:	Email:	Tel No.

[redacted]

Targeted follow up questionnaire for Osteonecrosis of the Jaw

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

Patient Identifier: _____ Patient Initials: _____ Date of this report: ___/___/_____

Gender: ☐ Male ☐ Female Weight: _____lb _____kg Age at the time of event: ___/___/_____

Date of event onset: ___/___/_____ Event reported term: _____

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

Denosumab Indication

☐ Postmenopausal osteoporosis

☐ Bone loss from hormone ablation therapy

Please specify diagnosis _____

_____

☐ Advanced cancer with bone metastasis

Please specify cancer_____

☐ Others

Please specify_____

_____

☐ Don't know

Denosumab Dose

☐ 60 mg SC every 6 months

☐ 120 mg SC every 4 weeks

☐ Other Please specify_____

☐ Don't know.

Denosumab Exposure

Denosumab first administered (date)_____

Last Denosumab dose before event (date)_____

☐Doses of denosumab skipped ☐Yes ☐No ☐ Unk

If yes, please specify_____

☐Doses of denosumab give after event began.

☐Yes ☐ No ☐ Unknown.

If yes, date of first dose following start of event_____

EVIDENCE OF EXPOSED BONE (Please indicate dates as DDIMMIYYYY)

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

☐No ☐Yes ☐Unknown; Please describe_____

☐Date exposed bone was first visualized/probed_____

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

☐No ☐Yes ☐Unknown; _____

Prior history of radiation therapy to jaw:

☐No ☐Yes ☐Unknown; _____

Prior history of metastatic disease to jaw:

☐No ☐Yes ☐Unknown; Please describe_____

Please indicate the location of involved area(s) on the diagram at right

(mark site(s) clearly with 'X').

Please describe location(s):

☐Right maxilla, teeth and lateral jaw ☐Left maxilla, teeth and lateral jaw

[redacted]

☐Right maxilla, medail jaw

☐Right mandible teeth and lateral jaw

☐Right mandible, medial jaw

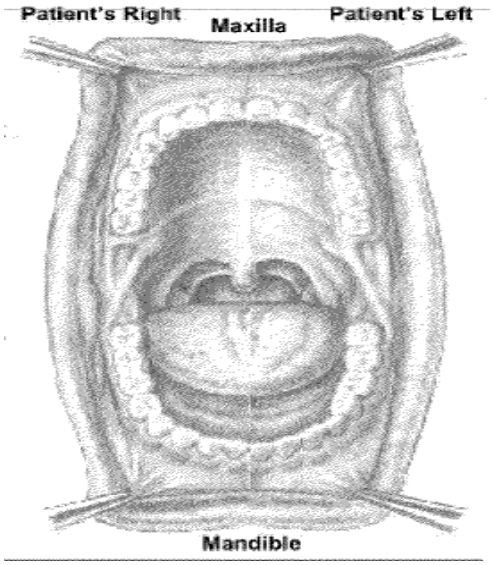
☐Maxilla hard palate

☐Left maxilla, medial jaw

☐Left mandible teeth and lateral jaw

☐Left mandjble, medial jaw

☐Other (specify)----------



Oral Findings

Evidence of infection:	☐No	☐Yes	☐Unknown
Please describe_____			
Exposed bone at the Site of extraction:	☐No	☐Yes	☐Unknown
Complete coverage of involved area(s) by mucosa	☐No	☐Yes	☐Unknown

If yes, date of complete mucosal coverage_____

CLINICAL. SYMPTOMS (Please indicate dates as DD/MM/YYYY)

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

Please describe the clinical sign/symptoms/location

_____

_____

_____

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

Dental oral surgery / stomatology consultations ☐NO ☐Yes ☐Unknown

If yes, give date of examination_____

Please provide any consult reports, radiographs. pictures if available

_____

[redacted]

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

Antibiotics ☐NO ☐Yes ☐Unknown; If yes, agent(s)/route/dose_____

Start date_____Stop date_____

Please describe outcomes of treatment_____

Oral rinses ☐NO ☐Yes ☐Unknown If yes, agent(s)/dose_____

Please describe outcomes of treatment_____

Oral Surgery ☐NO ☐Yes ☐Unknown If yes, type of surgery_____

Start date_____ Stop date_____

Please describe outcomes of treatment_____

Hospitalizations ☐NO ☐Yes ☐Unknown If yes, reason for hospitalization_____

Hospitalization begin date_____ Hospitalization end date_____

Please describe outcomes of treatment_____

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

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

If yes, please describe----------

Dental extraction recently ☐No ☐Yes ☐Unknown _____

If yes, please describe----------

Dental surgery recently ☐No ☐Yes ☐Unknown _____

If yes, please describe----------

Periodontal disease including gingival bleeding, calculus, etc ☐No ☐Yes ☐Unknown

Start date___/___/_____ Stop date___/___/_____

Draining fistula in affected area: ☐No ☐Yes ☐Unknown

Start date___/___/_____ Stop date___/___/_____

Dental abscess in affected area ☐No ☐Yes ☐Unknown

Start date___/___/_____ Stop date___/___/_____

Osteomyelitis in affected area ☐No ☐Yes ☐Unknown

Start date___/___/_____ Stop date___/___/_____

Root canal treatment near affected area ☐No ☐Yes ☐Unknown

If yes, date of treatment:___/___/_____

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

History of dentures/ dental appliance/ implant ☐NO ☐Yes ☐ Unknown

If yes, please specify ☐ Upper ☐ Lower

[redacted]

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

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

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

Start date_____ Stop date_____

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

Start date_____ Stop date_____

Glucocorticoid use within the past 12 months ☐No ☐Yes ☐Unknown

If yes, agent(s)/dose_____

Start date_____ Stop date_____

Immunosuppressant use within the past 12months ☐No ☐Yes ☐Unknown

If yes, agent(s)/dose_____

Start date_____ Stop date_____

Chemotherapy within the past 12 months ☐No ☐Yes ☐Unknown

If yes, agent(s)/dose_____

Start date_____ Stop date_____

Anti-angiogenic agents (e.g. bevacizumab) within the past 12 months ☐No ☐Yes ☐Unknown

If yes, agent(s)/dose_____

Start date_____ Stop date_____

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

Current smoker ☐No ☐Yes ☐Unknown

If yes, estimated number of pack-years_____

If past smoker, stop date_____

Alcohol consumption ☐No ☐Yes ☐Unknown

If yes, estimated drinks per weeks_____

Diabetes ☐ No ☐ Yes ☐ Unknown

If yes, ☐ Type I ☐ Type II

Patient Reminder Card Status (For EU Patients)

Received a patient reminder card prior to ONJ event:

☐Yes ☐No ☐Unknonwn

REPORTER DETAILS:

Name Title:	Signature	Date

[redacted]

Address: City: Country: State/Province: Postal code:	Email:	Tel No.

[redacted]

Targeted follow-up questionnaire for Potential Atypical Fracture

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

Patient Identifier: _____ Patient Initials: _____ Date of this report: ___/___/_____

Gender: ☐ Male ☐ Female Weight: _____lb _____kg Age at the time of event: ___/___/_____

Event reported term: _____

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

Denosumab Indication

☐ Postmenopausal osteoporosis

☐ Bone loss from hormone ablation therapy

Please specify diagnosis _____

_____

☐ Advanced cancer with bone metastasis

Please specify cancer_____

☐ Others

Please specify_____

_____

☐ Done know

Denosumab Dose

☐ 60 mg SC every 6 months

☐ 120 mg SC every 6 months

☐ Other Please specify_____

☐ Done know.

Denosumab Exposure

Denosumab first administered (date) ___/___/_____

Last Denosumab dose before event (date) ___/___/_____

☐Doses of denosumab skipped ☐Yes ☐No ☐ Unk

If yes, please specify_____

☐Doses of denosumab give after event began.

☐Yes ☐ No ☐ Unknown.

If yes, date of first dose following start of event___/___/_____

DIAGNOSIS (Check all that apply)

Location of fracture:

☐ Femur neck

☐ Femur distal

☐ Femur midshaft

☐ Femur intertrochanter

☐ Femur subtrochanter

☐ Other location (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)

☐ Minimal trauma other than a fall

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

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

☐ Unknown type of trauma

Diagnostic imagining 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)**

[redacted]

Was this pathological fracture associated with bone tumour or Miscellaneous bone disease (paget's disease, fibrous dysplasia)? ☐ Yes ☐ No ☐ Unknown Types of fracture ☐ Transverse ☐ Oblique ☐ Spiral Fracture radiology report include: Simple transverse or oblique (30) fracture with beaking of cortex: ☐ Yes ☐ No ☐ Not reported Diffuse cortical thickening of the proximal femoral shaft ☐ Yes ☐ No ☐ Not reported	Early symptom of pain over fracture site: ☐ Pain at site at rest ☐ Pain at site with weight bearing ☐ None ☐ Fracture healed (union) within 6 months ☐ Yes ☐ No ☐ Unknown If yes, ☐Date of fracture union (DD/MM/YYYY):___/___/_____ ☐ Patient able to walk without assistance: ☐Yes ☐ No ☐ Unknown ☐ Fracture union confirmed through imaging ☐Yes ☐ No ☐ Unknown If yes, check all diagnostic imaging that applies ☐ X-ray ☐ CT scan ☐ MRI

TREATMENT (Please provide dates and indicate attachments if available)

Methods to reduce and set fracture.

☐ Non-surgical reduction_____

☐ Casting _____

☐ Surgery _____

☐ Revision surgery (2nd surgery) _____

☐ Other _____

☐ Unknown _____

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

General

☐ History or current corticosteroid use

☐ Affected hip with prior surgical pinning

☐ Affected hip with prior hip replacement

Prior osteoporosis therapy:

☐ Estrogen

☐ Selective estrogen receptor modulator (SERM)

☐ Biphosponate (please indicate)

☐ Intravenous ☐ Oral

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

[redacted]

☐ 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 record/consults/radiology report attached? ☐ Yes ☐ No

_____

_____

_____

REPORTER DETAILS:

Name Title:	Signature	Date
Address: City: Country:	Email:	Tel No.

[redacted]

State/Province: Postal code:		

Targeted follow up questionnaire for Fracture Healing

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

Patient Identifier: _____ Patient Initials: _____ Date of this report: __/__/____

Gender: ☐ Male ☐ Female Weight: _____lb _____kg Age at the time of event: __/__/____

Event reported term: _____

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

Denosumab Indication

☐ Postmenopausal osteoporosis

☐ Bone loss from hormone ablation therapy

Please specify diagnosis _____

_____

☐ Advanced cancer with bone metastasis

Please specify cancer_____

☐ Others

Please specify_____

_____

☐ Done know

Denosumab Dose

☐ 60 mg SC every 6 months

☐ 120 mg SC every 6 months

☐ Other Please specify_____

☐ Done know.

Denosumab Exposure

Denosumab first administered (date)_____

Last Denosumab dose before event (date)_____

☐Doses of denosumab skipped ☐Yes ☐No ☐ Unk

If yes, please specify_____

☐Doses of denosumab give after event began.

☐Yes ☐ No ☐ Unknown.

If yes, date of first dose following start of event_____

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

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

☐ **Fracture to upper body (i.e., above waist)**

Specify location (check all that apply)

☐ Cervical spine
☐ Clavicle
☐ Hand/metacarpal/Phalange
☐ Head/face/skull
☐ Humerus
☐ Olecranon
☐ Radius
☐ Rib
☐ Scapula
☐ Shoulder
☐ Sternum
☐ Ulna
☐ Wrist/ Carpal

☐ **Fracture to lower body (i.e., below waist)**

Specify location (check all that apply):

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

[redacted]

☐ Other _____

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

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

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

☐ Non-traumatic

Characteristics of fracture (check all that apply):

☐ Comminuted

☐ Compound

☐ Pathologic

☐ Poor alignment

☐ Poor immobilization of Segments

☐ Soft tissue injury

☐ Unknown

TREATMENT (Please provide dates and indicate attachments if available)

Methods to reduce and set fracture (check all that apply):

☐ Casting _____

☐ Non-surgical reduction _____

☐ Revision surgery (2nd surgery) _____

☐ Surgery _____

☐ Traction _____

☐ Other _____

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

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

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

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

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

MEDICAL HISTORYIRISK FACTORS (Check all that apply, provide dates and attach relevant reports)

☐ Current smoker/tobacco use _____

_____

☐ History or current corticosteroid use _____

_____

☐ Prior fracture history _____

_____

☐ Diabetes _____

_____

_____

[redacted]

REPORTER DETAILS:

Title, Name & Surname	Occupation	Signature	Date
Postal Address: Postcode:	Email:	Tel No.	

Targeted follow up Questionnaire for Malignancy Adverse Events

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

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

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

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

If yes, date of prior cancer (DD/MM/YYYY): ___/___/ ____

Tumor stage, if known: _____

Primary site of malignancy: _____

TUMOR STAGE:

Tumor Size (Check which one applies):

TX ☐ TO ☐ Tis ☐ T1 ☐ T2 ☐ T3 ☐ T4 ☐

Tumor Grade (Check which one applies):

GX ☐ G1 ☐ G2 ☐ G3 ☐

Localized (no regional involvement/no distant metastasis)? Yes ☐ No ☐
(If yes, skip next 2 questions)

Lymph Node Involvement (Check which one applies):

NX ☐ N1 ☐ N2 ☐ N3 ☐

Metastases (Check which one applies):

MX ☐ MO ☐ M1 ☐

TREATMENT:

Hospitalized?	Yes ☐ No ☐ unknown ☐
ICU admission?	Yes ☐ No ☐ unknown
Overall length of hospital stay:	≤ 1 day ☐ ≥ 1 day or ≥ 7 Days ☐ > 7 Days ☐
Surgical treatment?	Yes ☐ No ☐ unknown ☐
Chemotherapy (includes biologics)?	Yes ☐ No ☐ unknown ☐
Hormonal treatment?	Yes ☐ No ☐ unknown ☐
Radiation treatment?	Yes ☐ No ☐ unknown ☐
Bone marrow transplant?	Yes ☐ No ☐ unknown ☐

If yes, autologous ☐ heterologous ☐

[redacted]

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

RISK FACTORS (Check all that apply):

Smoking ☐

Prior Malignancy ☐

Positive Family History (Check all that apply):

Same cancer ☐

Different cancer ☐

Prior therapeutic radiation exposure ☐

Environmental exposure ☐

Specify: _____

[redacted]

Targeted follow up questionnaire for Hypersensitivity

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

Patient Identifier: _____ Patient Initials: _____ Date of this report: ___/___/_____

Gender: ☐ Male ☐ Female Weight: _____lb _____kg Age at the time of event: ___/___/_____

Study number (if applicable): _____

Event reported term: _____

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

Denosumab Indication

☐ Postmenopausal osteoporosis

☐ Bone loss from hormone ablation therapy

Please specify diagnosis _____

_____

☐ Advanced cancer with bone metastasis

Please specify cancer_____

☐ Others

Please specify_____

_____

☐ Done know

Denosumab Dose

☐ 60 mg SC every 6 months

☐ 120 mg SC every 6 months

☐ Other Please specify_____

☐ Done know.

Denosumab Exposure

Denosumab first administered (date)_____

Last Denosumab dose before event (date)_____

☐Doses of denosumab skipped ☐Yes ☐No ☐ Unk

If yes, please specify_____

☐Doses of denosumab give after event began.

☐Yes ☐ No ☐ Unknown.

If yes, date of first dose following start of event_____

SIGN AND SYMPTOMS (Check all that apply)

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

EVALUATIONS, DIAGNOSIS & LABORATORY MEASURES (Please indicate and attach copy of report if available)

Diagnostic	Results/Units	Reference range/Units	Date	Report attached. Y/N
Results at BASELINE (Prior to Osvyrti)				
CBC with Differential				
WBC				
RBC				
Eosinophils				
Hgb				
Hct				

[redacted]

Platelets				
Other				
Albumin				
Total Protein				
BUN				
Serum Creatinine				
ALT				
AST				
ALP				
Bilirubin				
Calcium				
K+				
Na+				
Phosphorous				
Mg++				
Cl-				
CrCI				

Diagnostic	**Results/Units**	**Reference range/Units**	**Date**	**Report attached. Y/N**
Results at THE TIME OF EVENT				
CBC with Differential				
WBC				
RBC				
Eosinophils				
Hgb				
Hct				
Platelets				
Other				
Albumin				
Total Protein				
BUN				
Serum Creatinine				
ALT				
AST				
ALP				
Bilirubin				
Calcium				
K+				
Na+				
Phosphorous				
Mg++				
Cl-				
CrCI				

TREATMENT (Please provide dates and indicate attachments if available)

☐ ER corticosteroids Route ☐ IV ☐ Oral

☐ ER anti-histaminics Route ☐ IV only ☐ Oral only ☐ Both oral and IV

☐ Required hospital admission ☐ Yes ☐ No

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

☐ ICU admission ☐ Yes ☐ No ☐ Unknown

[redacted]

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

☐ In hospital corticosteroids Route ☐ IV only ☐ Oral only ☐ Both oral and IV

☐ In hospital anti-histaminics Route ☐ IV only ☐ Oral only ☐ Both oral and IV

☐ Other in hospital treatment

.☐ IV vasopressors ☐ Yes ☐ No ☐ Unknown

☐ Intubation/mechanical ventilation ☐ Yes ☐ No ☐ Unknown

CONCOMITANT MEDICATIONS

☐ ACE inhibitors ☐ IV contrast ☐ Allopurinol ☐ NSAIDS/aspirin

☐ Cancer chemotherapy ☐ Penicillamine ☐ Dapsone ☐ Rifampin

☐ Anticonvulsants (Check which apply):

☐ Phenytoin ☐ Carbamazepine ☐ Phenobarbital

☐ Antibiotics (Check which apply):

☐ Beta-lactams including penicillin and cephalosporin ☐ Macrolides

☐ Sulphonamides ☐ Quinolones.

☐ Hypersensitivity event resolved ☐ Yes ☐ No ☐ Unknown

If yes, date (DD/MM/YYYY):_____

☐ Final diagnosis or etiology (incl. Start date). Please send supporting documents for diagnosis:

_____

☐Other consult report (please indicate any attachments):

_____

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

_____

_____

_____

_____

REPORTER DETAILS:

Title, Name & Surname	Occupation	Signature	Date
Postal Address: Postcode:	Email:	Tel No.	

[redacted]

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

Prior to the launch of denosumab prescribing in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the Patient reminder card, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The MAH shall ensure that in each Member State where denosumab is marketed, all healthcare professionals and patients who are expected to prescribe and use denosumba have access to/are provided with the following educational material:

- Patient reminder card

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

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