EU Risk Management Plan
for
Jubereq 120 mg solution for injection
(Denosumab)

RMP version to be assessed as part of this application:

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Rationale for submitting an updated RMP: The Risk Management Plan (RMP) has been updated as per CHMP Day 120 Assessment Report.

Summary of significant changes in this RMP: Significant changes have been done in following sections of RMP: Part II (SVII and SVIII), Part III, Part V, Part VI and Part VII (Annex 4).

Other RMP versions under evaluation: None

Details of the currently approved RMP: None

QPPV name: Ms. Agata Gesiewicz

QPPV signature: (On behalf of QPPV)**:**

TABLE OF CONTENTS

TABLE OF CONTENTS **2**
LIST OF TABLES **4**
Part I: Product(s) Overview **5**
Part II: Safety specification **8**
Module SI - Epidemiology of the indication(s) and target population(s) 8
Module SII - Non-clinical part of the safety specification 8
Module SIII - Clinical trial exposure 8
Module SIV - Populations not studied in clinical trials 13
SIV.1 Exclusion criteria in pivotal clinical studies within the development programme 13
SIV.2 Limitations to detect adverse reactions in clinical trial development programmes 18
SIV.3: Limitations in respect to populations typically under-represented in clinical trial development programmes 18
Module SV - Post-authorisation experience 19
SV.1 Post-authorisation exposure 19
Module SVI - Additional EU requirements for the safety specification 19
Module SVII - Identified and potential risks 20
SVII.1: Identification of safety concerns in the initial RMP submission 20
SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP 20
SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP 21
SVII.2: New safety concerns and reclassification with a submission of an updated RMP 23
SVII.3: Details of important identified risks, important potential risks, and missing information 24
SVII.3.1. Presentation of important identified risks and important potential risks 24
SVII.3.2: Presentation of the missing information 43
Module SVIII - Summary of the safety concerns 45
Part III: Pharmacovigilance Plan (including post-authorisation safety studies) **46**
III.1 Routine pharmacovigilance activities 46
III.2 Additional pharmacovigilance activities 46
III.3 Summary Table of additional Pharmacovigilance activities 46
Part IV: Plans for post-authorisation efficacy studies **47**
Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities) **48**
V.1. Routine Risk Minimisation Measures 48
V.2. Additional Risk Minimisation Measures 52
V.3 Summary of risk minimisation measures 53
Part VI: Summary of the risk management plan **58**
I. The medicine and what it is used for 58
II. Risks associated with the medicine and activities to minimise or further characterise the risks 58
II.A List of important risks and missing information 59
II.B Summary of important risks 61
II.C Post-authorisation development plan 67
II.C.1 Studies which are conditions of the marketing authorisation 67

II.C.2 Other studies in post-authorisation development plan 67
Part VII: Annexes 68
Annex 1 – EudraVigilance Interface 69
Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme 69
Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan 69
Annex 4 - Specific adverse drug reaction follow-up forms 69
Annex 5 - Protocols for proposed and on-going studies in RMP part IV 79
Annex 6 - Details of proposed additional risk minimisation activities 80
Annex 7 - Other supporting data (including referenced material) 81
Annex 8 – Summary of changes to the risk management plan over time 81

LIST OF TABLES

Table 1: Product Overview....5
Table 2: Clinical studies with denosumab....9
Table 3: Subject Demographic data and baseline characteristics (Safety set, Main Phase)....10
Table 4. Subject Demographic data and baseline characteristics (Extension Phase, Safety set)....11
Table 5: Important exclusion criteria in pivotal clinical studies within the development programme....13
Table 6: Exposure of special populations included or not in clinical trial development programmes....18
Table 7: Risks considered important for inclusion in the list of safety concerns in the RMP....21
Table 8: Details of important identified risks....24
Table 9: Details of Important Potential Risks....32
Table 10: Details of Missing Information....43
Table 11: Summary of Safety concerns....45
Table 12: Description of routine risk minimisation measures by safety concern....48

Part I: Product(s) Overview

Table 1: Product Overview

Active substance(s) (INN or common name)	Denosumab
Pharmacotherapeutic group(s) (ATC Code)	**Pharmacotherapeutic group(s):** Drugs for treatment of bone diseases – Other drugs affecting bone structure and mineralization **ATC Code:** M05BX04
Marketing Authorisation Applicant	Accord Healthcare S. L.U., Spain [redacted]
Medicinal products to which this RMP refers	01
Invented name(s) in the European Economic area (EEA)/ [redacted]	Jubereq 120 mg solution for injection in vial
Marketing authorisation procedure	Centralised Procedure (EMEA/H/C/006398) [redacted]
Brief description of the product	Chemical class: Monoclonal IgG2 antibody
	Summary of mode of action: Denosumab is a human monoclonal antibody (IgG2) that targets and binds with high affinity and specificity to Receptor activator of nuclear factor kappa-B ligand (RANKL), preventing the RANKL/RANK interaction from occurring and resulting in reduced osteoclast numbers and function, thereby decreasing bone resorption and cancer-induced bone destruction.
	Important information about its composition:

	Each vial contains 120 mg of denosumab in 1.7 mL of solution (70 mg/mL). Excipient with known effect Each 1.7 mL of solution contains 78.2 mg sorbitol (E420)
Hyperlink to the Product Information	Refer Module 1.3.1 for Product Information
Indication(s) in the EEA	*Current:* Prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with advanced malignancies involving bone. Treatment of adults and skeletally mature adolescents with giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity.
Dosage in the EEA	*Current:* **Posology:** Supplementation of at least 500 mg calcium and 400 IU vitamin D daily is required in all patients, unless hypercalcaemia is present. *Prevention of skeletal related events in adults with advanced malignancies involving bone* The recommended dose is 120 mg administered as a single subcutaneous injection once every 4 weeks into the thigh, abdomen or upper arm. *Giant cell tumour of bone* The recommended dose of Jubereq is 120 mg administered as a single subcutaneous injection once every 4 weeks into the thigh, abdomen or upper arm with additional 120 mg doses on days 8 and 15 of treatment of the first month of therapy.

	Patients in the phase II study who underwent complete resection of giant cell tumour of bone did receive an additional 6 months of treatment following the surgery as per study protocol. **Method of administration:** For subcutaneous use.
Pharmaceutical form(s) and strengths	*Current:* Solution for injection 120 mg/1.7 ml (70 mg/ml)
Is the product subject to additional monitoring in the EEA[redacted]?	No

Part II: Safety specification

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

Not applicable

Module SII - Non-clinical part of the safety specification

There were no non-clinical studies performed for Jubereq 120 mg solution for injection.

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.

Jubereq (containing 120 mg of denosumab solution for injection in vial) has been developed as a proposed biosimilar to both the US-licensed and EU-approved Xgeva.

There was no separate clinical study conducted for Jubereq 120 mg but the MAH has conducted a study of Osvyrti 60 mg solution for injection in pre-filled syringe (Protocol No. 0774-19) and MAH has presented the data in this RMP by referring the same study (Protocol No. 0774-19).

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 denosumab

Clinical Study Design	Study treatment	Comment
Phase III (Protocol No. 0774-19) 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 (60 mg/mL) **Reference product:** Prolia® solution for injection in single-use prefilled syringe (Denosumab)	**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 =

Clinical Study Design	Study treatment	Comment
		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	

		Statistics	Denosumab (N=276)	Prolia (N=276)	Total (N=552)	p-value
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 treatment status	Present	n (%)	7 (2.5)	7 (2.5)	14 (2.5)	1.0000
	Absent	n (%)	269 (97.5)	269 (97.5)	538 (97.5)	

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)	

		Statistics	Denosumab (N=62)	Prolia (N=61)	Total (N=123)	p-value
	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)	
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

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 known allergies, hypersensitivity, or intolerance to denosumab or its excipients.	Standard exclusion criteria as per study protocol	No	Jubereq is contraindicated in patients with hypersensitivity to denosumab or to any of the excipients. These conditions could potentially interfere with the aim/ results of the study, or it can have impact on patient safety.
2. Documented medical history and/or current evidence of any of the following oral/dental conditions: a) Prior history or current evidence of osteomyelitis	Standard exclusion criteria as per study protocol	No	Jubereq is contraindicated in presence of unhealed lesions from dental or oral surgery. These conditions could potentially

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.			interfere with the aim/ results of the study, or it can have impact on patient safety.
3. 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. 4. 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	Jubereq is contraindicated in presence of severe, untreated hypocalcaemia. These conditions could potentially interfere with the aim/ results of the study, or it can have impact on patient safety.

example celiac disease, history of excision of small intestine etc.) and severe renal impairment). 5. 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. 6. 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. 7. 25 (OH) Vitamin D lower than 20 ng/mL as assessed by the central laboratory at Screening. Vitamin D repletion will be permitted, and participants may be rescreened once.			

8. Documented medical history of 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. 9. History of external beam or implant radiation therapy involving the skeleton. 10. History and /or presence of 1 severe fracture or 2 moderate vertebral fractures. 11. Patients with bone metastases or a history of malignancies affecting bones. 12. Lymphoma, leukemia, or any malignancy (current or suspected) within the past 5 years except for basal cell or 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	Standard exclusion criteria as per study protocol	No	These conditions could potentially interfere with the aim/ results of the study or it canhave impact on patient safety.

cured with minimal risk of recurrence. 13. 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 month of cumulative use between 6 and 12 months prior to randomization 14. Teriparatide or any PTH analogs treatment received within 12 months prior to randomization. 15. Received any investigational IMP 30 days or 5 half-lives (whichever is longer) before the 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 • Patients with a disease severity different from inclusion criteria in clinical trials • Immunocompromised patients	Not included in the clinical development program
Population with relevant different ethnic origin	Not included in the clinical development program.
Subpopulations carrying relevant genetic polymorphisms	No specific exclusions.
Other	Not applicable

Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

Not applicable as product is not yet launched.

Module SVI - Additional EU 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.

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):

- Lichenoid drug eruptions, 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:

- Drug hypersensitivity and Anaphylactic reaction, frequency: rare (≥ 1/10,000 to < 1/1,000). These both are listed events 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 whichthe risk minimisation messages in the product information are adhered by prescribers (e.g. actionsbeing part of standard clinical practice):

- 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 Jubereq, 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 Risk	
Osteonecrosis of jaw(ONJ)	In clinical trials, the incidence of ONJ was higher with longer duration of exposure; ONJ has also been diagnosed after stopping treatment with denosumab with the majority of cases occurring within 5 months after the last dose. 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 Jubereq administration.
Atypical femoral fracture	Atypical femoral fractures may occur with little or no trauma in the subtrochanteric and diaphyseal regions of the femur. The event is reported 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 several months after the last dose in patients with giant cell tumor of bone and in patients with growing skeletons	Clinically significant hypercalcemia requiring hospitalization and complicated by acute renal injury has been reported in denosumab-treated patients with giant cell tumor of bone, weeks to months following treatment discontinuation in post marketing report.
Important Potential Risks	
Cardiovascular events	Cardiovascular events have not been reported in pre-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 tumor 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.
Delay in diagnosis of primary malignancy in giant cell tumor of bone	Malignancy in giant cell tumor of bone or progression to metastatic disease is an infrequent event and a known risk in patients with giant cell tumor of bone. 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 giant cell tumor of bone patients treated with denosumab.
Hypercalcemia several months	Clinically significant hypercalcemia after treatment

after the last dose in patients other than those with giant cell tumor of bone or growing skeletons	discontinuation has been reported in the post-marketing setting in pediatric patients.
Missing information	
Patients with prior intravenous bisphosphonate treatment	Long-term antiresorptive treatment (including both denosumab and bisphosphonates) may contribute to an increased risk for adverse outcomes such as osteonecrosis of the jaw and atypical femur fractures due to significant suppression of bone remodelling.
Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumor of bone	As per clinical studies data, efficacy results in skeletally mature adolescents were similar to those observed in adults. However, there are no data available for long-term treatment and long-term follow-up after treatment.
Off-label use in patients with giant cell tumor of bone that is resectable where resection is unlikely to result in severe morbidity	There was no information available for off-label use of denosumab in patients with giant cell tumor of bone that is resectable where resection is unlikely to result in severe morbidity

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: Osteonecrosis of jaw	
MedDRA terms (Preferred Terms)	Osteonecrosis of jaw
Potential mechanisms	Osteonecrosis of the jaw (ONJ) appears to be multifactorial and multiple hypotheses have been postulated and have included factors such as inhibition of bone remodeling, infection and inflammation, inhibition of angiogenesis, soft tissue toxicity, altered immunity and genetic predisposition. As yet, evidence supporting these hypotheses has been variable and little is understood in how these multiple pathways might interact.[1].
Evidence source(s) and strength of evidence	This risk was identified in randomized, controlled, phase 3 clinical trials. This risk was further supported by post-marketing reports.[1]
Characterization of the risk	In-line with XGEVA RMP, risk has been characterized as follows: Frequency: In the primary treatment phases of three phase III active-controlled clinical trials in patients with advanced malignancies involving bone, ONJ was confirmed in 1.8% of patients treated with denosumab (median exposure of 12.0 months; range: 0.1 – 40.5) and 1.3% of patients treated with zoledronic acid. In a phase III trial in patients with non-metastatic prostate cancer (a patient population for which denosumab is not

[1] Risk Management Plan of Xgeva ® (Denosumab), dated 07-Jul-2021. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/xgeva

	indicated), with longer treatment exposure of up to 7 years, the patient-year adjusted incidence of confirmed ONJ was 1.1 per 100 patient-years during the first year of treatment, 3.0 in the second year, and 7.1 thereafter. The trials in patients with breast or prostate cancer included a denosumab extension treatment phase (median overall exposure of 14.9 months; range: 0.1 – 67.2). ONJ was confirmed in 6.9% of patients with breast cancer and prostate cancer during the extension treatment phase[2] Severity: Most events leading to adjudication as ONJ were assessed as moderate to severe. Life-threatening events have been reported. Reversibility: In general, ONJ events are clinically reversible. The majority of ONJ cases resolve with denosumab treatment interruption or discontinuation. Surgical treatment may be required; bone resection is not usually necessary. Long-term outcomes: No data on long-term outcomes are available Impact on quality of life: Discomfort associated with ONJ lesions and/or with more extensive treatments may impact patient wellbeing via decreased oral intake (eg, decreased hydration and decreased nutritional intake).
Risk factors and risk groups	Risk factors associated with ONJ include the use of antiresorptives (particularly amino-bisphosphonates delivered by intravenous [IV] dosing), older age, poor dental hygiene, periodontal disease, invasive dental

[2] SmPC and PIL of Jubereq (Denosumab)

	procedures, trauma from poorly fitting dentures, malignancy, chemotherapy (including anti-angiogenesis agents such as bevacizumab), radiation to head and neck, corticosteroids, hypercoagulable state secondary to underlying malignancy, smoking and vascular insufficiency due to thrombosis.[1]
Preventability	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 Jubereq administration.[2]
Impact on the risk-benefit balance of the product	The risk of ONJ events has been considered in the product benefit-risk assessment. In light of the product labeling and a patient reminder card that has been proposed to minimize this risk, the overall benefit-risk balance is considered to be positive.[1]
Public health impact	Significant public health impact is not expected based on the relative frequency observed in clinical trials and with the observations that most ONJ events appear to be moderate to severe in severity and resolve without requiring extensive surgical treatment.[1]
Important identified risk: Atypical femoral fracture	
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 causes of AFF are likely multifactorial. Based on nonclinical studies of bisphosphonates, 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.[1]
Evidence source(s) and strength of evidence	This risk was identified in randomized, controlled, phase 3 clinical trials and in open-label, phase 2 clinical trials. This risk was further supported by post-marketing reports.[1]
Characterization of the risk	<u>In-line with XGEVA RMP, risk has been characterized as follows:</u> <u>Frequency:</u> In a comprehensive evaluation of denosumab 120 mg clinical trials, 15 subjects experienced 17 events meeting the American Society for Bone and Mineral Research criteria for AFF. This corresponds to 0.2% (15 of 8342) of all subjects who received at least 1 dose of denosumab (Similar results are observed when consideration is limited to studies utilizing monthly dosing throughout [0.1 %, 6 subjects with AFF in 6101 subjects]). All of these adjudicated events of AFF occurred in subjects who received denosumab 120 mg for at least 4 years corresponding to 0. 7% (15 of the 2228) of subjects who were followed for 4 or more years. In the clinical trial program, AFF has been reported uncommonly in patients treated with denosumab 120 mg and the risk increased with longer duration of treatment. Events have occurred during treatment and up to 9 months after treatment was discontinued. <u>Severity:</u>

	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. Reversibility: It is unknown if the pathophysiological mechanism(s) contributing to the development of AFF are reversible after treatment is discontinued. Long-term outcomes: No data on long-term outcomes are available. Impact on quality of life: As with other hip 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.
Risk factors and risk groups	Atypical femoral fractures have also been reported in patients with certain comorbid conditions (e.g. vitamin D deficiency, rheumatoid arthritis, hypophosphatasia) and with use of certain pharmaceutical agents (e.g. bisphosphonates, glucocorticoids, proton pump inhibitors).[2]
Preventability	Discontinuation of denosumab therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient based on an individual benefit risk assessment. 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.[2]
Impact on the risk-benefit balance ofthe product	The risk of AFF events has been considered in the product benefit-risk assessment. In light of the product labeling that has been proposed to minimize this risk, the overall benefit-

	risk balance is considered to be positive.[1]
Public health impact	Based on the frequency of AFF, the size of the indicated populations, and usage patterns of denosumab in clinical practice, no significant additional public health impact is expected.[1]
Important identified risk: Hypercalcemia several months after the last dose in patients with giant cell tumor of bone and in patients with growing skeletons	
MedDRA terms	Hypercalcemia
Potential mechanisms	The mechanism(s) of hypercalcemia several months after the last dose of denosumab in patients with GCTB and in patients with a growing skeleton are not well characterized, but may be a consequence of the following, alone, or in combination: Denosumab treatment and resultant RANK/RANKL pathway inhibition in adults with giant-cell containing lesions such as GCTB leads to histopathologic evidence of a dramatic decrease in osteoclast-like giant cells which is complemented by woven bone formation and calcification within the tumors and even at sites of distant metastases. It is possible this calcium could serve as a depot that is mobilized with reactivation of tumor-associated, RANKL driven giant cell mediated osteolysis following cessation of denosumab. • Hypercalcemia may result from rapid resorption of retained primary spongiosa in a skeleton with active endochondral ossification such as in patients with a growing skeleton. The rate of endochondral ossification and duration of exposure to denosumab would determine the amount of accumulated primary spongiosa that could influence the

	magnitude of resorptive response (mechanostat-driven) and release of calcium from the skeleton either near the growth plates (as can be the case with the young adult and adolescent patients) or from the giant cell tumors themselves that have partially ossified in the cases of the adult patients with tumor recurrence via an autocrine/paracrine mechanism. • The magnitude of the resorptive response following treatment withdrawal in the patients with GCTB and in those with an immature skeleton could be dictated by the normal high rate of bone turnover within the GCTB lesion or in the growing skeleton of young patients. The response of the osteoclast lineage to loss of inhibition of osteoclasto-genesis may be intrinsically more robust in young individuals or may be affected by intratumor signaling pathways (eg, parathyroid hormone-related protein) in GCTB.[1]
Evidence source(s) and strength of evidence	This risk was identified in phase 2 clinical trials of adolescent and adult patients with GCTB, and in post-marketing reports of pediatric patients using denosumab for unauthorized indications[1].
Characterization of the risk	In-line with XGEVA RMP, risk has been characterized as follows: <u>Frequency</u>: Based on the 4 relevant clinical trial case reports (2 adults and 2 adolescents) identified from the completed Amgen clinical Study 20062004 of subjects with GCTB (526 subjects having received at least 1 dose of denosumab), the frequency of hypercalcemia in patients with GCTB following discontinuation of denosumab is 0.8 events per

	100 subjects which corresponds to an uncommon frequency (~ 0.1 and < 1 event per 100 subjects). In addition, clinically significant cases of post-treatment hypercalcemia have been identified from literature case reports of denosumab use in pediatric patients for unapproved indications such as fibrous dysplasia, aneurysmal bone cysts, and juvenile Paget's disease. Severity: In the GCTB study, the events of hypercalcemia in the 4 subjects from Study 20062004 were considered grade 2, 3, or 4 in severity. All subjects had acute renal injury, and all were hospitalized. Three of 4 subjects had more than 1 event. The severity of the events in the post-marketing literature case reports appears qualitatively similar. Reversibility: Hypercalcemia is reversible with appropriate supportive therapy. Long-term outcomes: No data on long-term outcomes are available. Impact on quality of life: Patients may present with severe hypercalcemia requiring hospitalization. Patients who experience hypercalcemia may develop complications such as acute renal injury.
Risk factors and risk groups	Patients with GCTB and young patients with growing skeletons following discontinuation of denosumab. In general, the most common cause of hypercalcemia in humans is hyperparathyroidism, particularly among women and individuals aged 65 years or older. Hyperthyroidism and rhabdomyolysis associated with renal failure also increase the risk of hypercalcemia, as does the ingestion of large of

	amounts of calcium through dairy products or more recently liberal use of calcium supplements.[1]
Preventability	No preventive measures are known. Monitor patients for signs and symptoms of hypercalcemia and treat them appropriately. Periodic serum calcium assessments should be given to at-risk patients as clinically indicated. The need for calcium and vitamin D supplementation should be reassessed if denosumab is discontinued.[1]
Impact on the risk-benefit balance of the product	The risk of hypercalcemia events several months after the last dose in patients with GCTB and in patients with growing skeletons has been considered in the product benefit-risk assessment. In light of the product labeling that has been proposed to minimize this risk, the overall benefit-risk balance is considered to be positive.[1]
Public health impact	No significant public health impact is expected as hypercalcemia several months after the last dose in patients with GCTB occurs uncommonly and GCTB is a rare tumor. Off-label use of denosumab in pediatric patients appears to be limited to rare conditions for which there is significant unmet medical need.[1]

Table 9: Details of Important Potential Risks

Important potential risk: Cardiovascular events	
MedDRA terms	Cardiac disorders (SOC), Vascular disorders (SOC)
Potential mechanisms	Elevated levels of osteoprotegerin (OPG) have been associated with coronary artery disease in cross-sectional studies, but this association has been contradicted by preclinical and epidemiological studies demonstrating that the lack of OPG or unopposed RANKL is associated with cardiac

	calcification. Because of these conflicting results and because denosumab inhibits RANKL, a theoretical concern for denosumab to affect progression of atherosclerosis exists[1].
Evidence source(s) and strength of evidence	The risk of cardiovascular (CV) events is a regulatory concern based on the epidemiological association between OPG levels and CV disease in man. Clinical data have not substantiated a cause-and-effect between OPG and atherosclerotic processes nor between denosumab or inhibition of RANKL and undesirable CV outcomes.[1]
Characterization of the risk	In-line with XGEVA RMP, risk has been characterized as follows: <u>Frequency</u>: In the pooled pivotal SRE Solid Tumor studies, subject incidence of CV adverse events was 29.7% in both treatment groups; the hazard ratio was 0.98 (95% Cl: 0.89, 1.08). In a pivotal study with denosumab 120 mg Q4W in subjects with CRPC (Study 20050147), the subject incidence of CV adverse events was 33.1 % in the denosumab group and 27.0% in the placebo group; the hazard ratio was 1.23 (95% Cl: 1.02, 1.49). In the SRE multiple myeloma study, the subject incidence of adverse events of cardiac disorders was 11.6% in the denosumab group and 13.5% in the zoledronic acid group; the hazard ratio was 0.85 (95% Cl:0.65, 1.12). The subject incidence of adverse events of vascular disorder was 20.9% in the denosumab group and 19.8% in the zoledronic acid group; the hazard ratio was 1.07 (95% Cl: 0.86,

	1.31). Severity: The majority of CV events were mild to moderate. Life-threatening and fatal events have been reported Reversibility: No data on reversibility are available. Long-term outcomes: No data on long-term outcomes are available Impact on quality of life: Cardiovascular disease varies greatly in severity. For severe disease, patients may be hospitalized for treatment and disability may occur
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 CV conditions and, thus, a higher incidence of CV toxicities than that of the general population. Risk factors for atherosclerosis include age, gender, ethnicity, family history, elevated lipid levels, cigarette smoking, hypertension, diabetes, and concomitant medications, including antipsychotic agents and cyclooxygenase-2 (COX-2) inhibitors.[1]
Preventability	Based on clinical data to date, denosumab has not been associated with an increased incidence or severity of CV adverse effects; therefore, no preventive measures are defined. Patients with potential CV events should be managed according to usual standards of care.[1]

Impact on the risk-benefit balance ofthe product	The risk of CV events has been considered in the product benefit-risk assessment, and the overall benefit-risk balance is considered to be positive.[1]
Public health impact	Significant public health impact on CV disease severity or incidence is not expected based on the information from denosumab clinical studies in the advanced cancer and postmenopausal osteoporosis (PMO)/hormone ablation therapy (HALT} settings.[1]
Important potential risk: Malignancy	
MedDRA terms	Malignancies (SMQ)
Potential mechanisms	The risk of malignancy is a theoretical concern that RANKL inhibition may lead to an increased risk for a new primary malignancy (NPM) by impairing immune surveillance mechanisms.[1]
Evidence source(s) and strength of evidence	Imbalance is observed in the NPM events between the zoledronic acid and Denosumab treatment groups in the pivotal clinical studies. The results of Study 20170728, a post-marketing retrospective cohort study, showed NPM incidence rates for Denosumab were generally lower than those for zoledronic acid in unadjusted analyses, suggesting no obvious excess risk associated with Denosumab [1]
Characterisation of the risk	In-line with XGEVA RMP, risk has been characterized as follows: <u>Frequency</u>: In the primary, double-blind treatment phases of 4 phase 3 active-controlled clinical trials in patients with advanced malignancies involving bone, NPM was reported in 54/3691 (1.5%) of patients treated

	with Denosumab (median exposure of 13.8 months; range: 1.0 to 51.7) and 33/3688 (0.9%) of patients treated with zoledronic acid (median exposure of 12.9 months; range: 1.0 to 50.8). The cumulative incidence at 1 year was 1.1 % for denosumab and 0.6% for zoledronic acid, respectively. In the SRE multiple myeloma study, the subject incidence of adverse events of NPM was 2.6% in the denosumab group and 1.4% in the zoledronic acid group; the hazard ratio was 1.81 (95% Cl: 0.90, 3.66). Subjects who had new malignancies in this study generally had underlying risk factors for malignancy and no pattern was apparent in the types of new primary malignancies. In clinical Study 20062004 in GCTB, based on medical review and a data cut-off date of the final analysis of 15 August 2018, a total of 20 subjects (3.8%; N = 526) developed new malignancy in GCTB. Of these 20 subjects, 9 subjects developed new malignancies that were unrelated to GCTB: 2 events (0.4%) of ductal breast carcinoma and single events of each, adenocarcinoma of colon, breast cancer stage I, neoplasm, oesophageal adenocarcinoma, osteosarcoma, papillary thyroid cancer, renal cancer, rhabdomyosarcoma, and thyroid cancer. A total of 11 subjects (2.1 %) developed new malignancy in GCTB: 5 subjects were deemed to have had primary malignant GCTB, 5 subjects were assessed to have had sarcomatous transformation, and 1 subject had secondary malignant GCTB (post-radiation). In Study 20170728, a retrospective observational

	cohort study of 9710 patients with bone metastases from breast, prostate, or lung cancer treated with Denosumab or IV zoledronic acid, the overall rate of NPM for the breast cancer cohort was 11.5 per 1000 person-years of follow-up (PY) in the Denosumab group and 16.2 per 1000 PY in the zoledronic acid group; for the prostate cancer cohort was 19.6 per 1000 PY in the Denosumab group and 20.1 per 1000 PY in the zoledronic acid group; and for the lung cancer cohort was 9.5 per 1000 PY in the Denosumab group and 11.5 per 1000 PY in the zoledronic acid group. The 3-year cumulative incidence of NPM for the breast cancer cohort was 0.022 (95% Cl: 0.014, 0.035) in the Denosumab group and 0.032 (95% Cl: 0.023, 0.045) in the zoledronic acid group; for the prostate cancer cohort was 0.034 (95% Cl: 0.026, 0.044) in the Denosumab group and 0.036 (95% Cl: 0.026, 0.049) in the zoledronic acid group; and for the lung cancer cohort was 0.007 (95% Cl: 0.004, 0.012) in the Denosumab group and 0.008 (95% Cl: 0.005, 0.014) in the zoledronic acid group. Severity: Not applicable. Reversibility: No data on reversibility are available. Long-term outcomes: No data on long-term outcomes are available. Impact on quality of life: Malignancy is typically disabling and may require

	surgery, chemotherapy, and/or radiotherapy.
Risk factors and risk groups	General factors for increasing risk of NPM include advancing age, diet, cigarette smoking, excessive ethanol consumption, and numerous environmental toxins. In addition, advanced cancer populations are at increased risk for NPM because of their existing malignancy, possible genetic predisposition, and exposure to chemotherapy and radiation treatment.[1]
Preventability	Second malignant neoplasms have become increasingly recognized and current recommendations include vigilance for these cancers in adult cancer survivors.[1]
Impact on the risk-benefit balance ofthe product	The risk of malignancy events has been considered in the product benefit-risk assessment. In light of the product labeling that has been proposed to minimize this risk, the overall benefit-risk balance is considered to be positive.[1]
Public health impact	Significant public health impact is not expected based on the information from studies in the PMO/HALT and advanced cancer settings.[1]
Important potential risk: Delay in diagnosis of primary malignancy in giant cell tumor of bone	
MedDRA terms	Second primary malignancy
Potential mechanisms	Due to well described sampling error at the time of GCTB diagnosis, primary malignancy in giant cell tumor of bone (PMGCTB) may be missed and benign GCTB may be presumed. Based on the mechanism of action and pathology of GCTB, denosumab is only expected to treat benign GCTB. However, there was

	a theoretical concern that treatment of an undiagnosed PMGCTB with denosumab could delay the diagnosis of PMGCTB.[1]
Evidence source(s) and strength of evidence	The risk of delay in diagnosis of PMGCTB is a regulatory concern based on the difficulties in diagnosing PMGCTB in Study 20062004. [1]
Characterization of the risk	In-line with XGEVA RMP, risk has been characterized as follows: Frequency: In clinical studies in GCTB, based on medical review, 11 subjects (2.1 %; N = 523) had GCTB bone malignancies. Of these, 5 subjects (1.0%) had PMGCTB. Severity: Not applicable. Reversibility: Not applicable. Long-term outcomes: No data on long-term outcomes are available. Impact on quality of life: Malignancy is typically disabling and may require surgery, chemotherapy, and/or radiotherapy.
Risk factors and risk groups	Patients with GCTB are known to be at risk for PMGCTB.[1]
Preventability	No preventive measures are known.
Impact on the risk-benefit balance ofthe product	The risk of delay in diagnosis of PMGCTB events has been considered in the product benefit-risk

	assessment. In light of the product labeling that has been proposed to minimize this risk, the overall benefit-risk balance is considered to be positive.[1]
Public health impact	Given that GCTB is very rare condition, no impact on public health is expected.[1]
Important potential risk: Hypercalcemia several months after the last dose in patients other than those with giant cell tumor of bone or growing skeletons	
MedDRA terms	Hypercalcemia
Potential mechanisms	The pathogenesis of hypercalcemia several months after the last dose in patients other than those with GCTB or growing skeletons may be a consequence of the transient increase in bone turnover activity. Upon cessation of denosumab, the disinhibition of RANKL allows for terminal differentiation and activation of osteoclasts, which were suppressed during treatment. In patients with underlying causes for calcium dyscrasias (i.e., subclinical hyperparathyroidism), denosumab discontinuation, with its transient increase in bone remodeling and accompanying release of bone mineral, could theoretically be associated with transient hypercalcemia in susceptible individuals if the normal homeostatic mechanism regulating serum calcium are not appropriately maintained.[1]
Evidence source(s) and strength of evidence	Hypercalcemia several months after the last dose in patients other than those with GCTB or growing skeletons is a theoretical concern based on the identified risk in other specific populations, GCTB, and pediatric populations[1]

Characterization of the risk	In-line with XGEVA RMP, risk has been characterized as follows: Frequency: Cases of hypercalcemia in the off-treatment period have been reported in clinical studies, but given the disease state of the subjects, as well as other confounding factors, the occurrence of hypercalcemia in patients other than those with GCTB or with growing skeletons cannot be attributed to discontinuation of denosumab based on available information. As the mechanism for the identified risk in the susceptible populations is not well understood, a theoretical risk remains in other patient groups. Severity: Not applicable. Reversibility: No data on reversibility are available. Long-term outcomes: No data on long-term outcomes are available. Impact on quality of life: Patients may present with severe hypercalcemia requiring hospitalization. Patients who experience hypercalcemia may develop complications such as acute renal injury.
Risk factors and risk groups	Patients other than those with GCTB or growing skeletons following cessation of denosumab.[1]
Preventability	No preventive measures are known.[1]

Impact on the risk-benefit balance of the product	The risk of hypercalcemia events following treatment discontinuation in patients other than those with GCTB or growing skeletons has been incorporated in the product benefit-risk assessment, and the overall benefit-risk balance remains positive.[1]
Public health impact	No significant public health impact is expected as the potential events remain infrequent despite extensive market exposure.[1]

SVII.3.2: Presentation of the missing information

Table 10: Details of Missing Information

Missing information: Patients with prior intravenous bisphosphonate treatment	
Evidence source	The incidence of ONJ in patients with prior IV bisphosphonate use was similar to that of patients who only received denosumab in the completed Study 20101363. No notable association was evident between ONJ and prior use of bisphosphonates.[1]
Population in need of further characterization	There is information from studies in patients with cancer showing that there is no increased risk of serious complications caused by bone metastases in patients who received denosumab following treatment with bisphosphonates. However, more information is needed.[1]
Missing information: Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumor of bone	
Evidence source	The overall safety profile of denosumab in the completed Study 20062004 was similar to the safety profile of denosumab observed in the treatment of subjects with advanced cancer and bone metastases.[1]
Population in need of further characterization	Information on safety with long-term treatment and with long-term follow-up in adults or adolescents with GCTB will be monitored by routine pharmacovigilance activities.[1]
Missing information: Off-label use in patients with giant cell tumor of bone that is respectable where resection is unlikely to result in severe morbidity	
Evidence source	No formal studies have been completed to determine denosumab's effect on off-label use in patients with

	GCTB that is resectable where resection is unlikely to result in severe morbidity.[1]
Population in need of further characterization	Information is not available on safety in patients with GCTB that is further characterization resectable where resection is unlikely to result in severe morbidity.[1]

Module SVIII - Summary of the safety concerns

Table 11: Summary of Safety concerns

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

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

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities as stated in the Pharmacovigilance System Master File (PSMF) are sufficient for the safety concerns mentioned in "Module SVIII - Summary of the safety concerns".

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 Jubereq (Denosumab).

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

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

- Osteonecrosis of jaw
- Atypical femur fracture

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

- To monitor the reporting rate and nature of ONJ in patients treated with Jubereq (Denosumab) in the post-marketing environment.
- To monitor the reporting rate and nature of AFF in patients treated with Jubereq (Denosumab) in the post-marketing 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

None proposed

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 12: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimization activities
Important Identified Risks	
Osteonecrosis of jaw	*Routine risk communication*: • SPC Sections: 4.3, 4.4, 4.8 and 5.1 • PL Section: 2 and 4 *Routine risk minimisation activities recommending specific clinical measures to address the risk*: • Recommendations for oral examination, maintenance of good oral hygiene during treatment, management of patients with unavoidable invasive dental procedure, and temporary interruption of treatment if ONJ occurs are included in Section 4.4 of SmPC. *Other routine risk minimisation measure beyond the Product Information:* • The prescription only status of the product.
Atypical femoral fracture	*Routine risk communication*: • SPC Sections 4.4 and 4.8 • PL Sections: 2 and 4 *Routine risk minimisation activities recommending specific clinical measures to address the risk*: • Recommendation for reporting new or unusual thigh, hip, or groin pain is included Section 4.4 of SmPC.

	Other routine risk minimisation measure beyond the Product Information: • The prescription only status of the product.
Hypercalcemia several months after the last dose in patients with giant cell tumor of bone and in patients with growing skeletons	*Routine risk communication:* • SPC Sections: 4.4 and 4.8 • PL Sections: 2 and 4 *Routine risk minimisation activities recommending specific clinical measures to address the risk*: • Recommendations for monitoring the patients for signs and symptoms of hypercalcaemia after discontinuation of Jubereq treatment are included in Section 4.4 of SmPC and Section 4 of the PL. *Other routine risk minimisation measure beyond the Product Information*: • The prescription only status of the product
Important Potential Risks	
Cardiovascular events	*Routine risk communication*: • None *Routine risk minimisation 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*: • SmPC Sections: 4.4, 4.8 and 5.1 • PL sections: 4

	Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendations for monitoring the patients for radiological signs of malignancy, new malignancy, or osteolysis are included in Section 4.4 of SmPC. *Other routine risk minimisation measure beyond the Product Information*: • The prescription only status of the product
Delay in diagnosis of primary malignancy in giant cell tumor of bone	*Routine risk communication*: • None *Routine risk minimisation 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
Hypercalcemia several months after the last dose in patients other than those with giant cell tumor of bone or growing skeletons	*Routine risk communication*: • None *Routine risk minimisation 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	
Patients with prior intravenous bisphosphonate treatment	*Routine risk communication*: • SmPC Sections: 4.5 and 5.1 • PL Section: 2 *Routine risk minimisation 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
Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumor of bone	*Routine risk communication*: • None *Routine risk minimisation 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
Off-label use in patients with giant cell tumor of bone that is resectable where resection is unlikely to result in severe morbidity	*Routine risk communication*: ➢ None *Routine risk minimisation 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

V.2. Additional Risk Minimisation Measures

In line with reference medicinal product, Additional Risk Minimisation Measures (aRMMs) have been proposed for risk Osteonecrosis of jaw:

Objectives	Patient reminder card will be distributed to address the following risk: • Osteonecrosis of jaw
Rationale for the additional risk minimization activity	The purpose of the Patient Reminder Cards is to remind patients about important safety information that they need to be aware of before and during treatment with denosumab (Jubereq) injections for cancer-related conditions, including: • To tell their doctor/nurse if they have any problems with their mouth or teeth before starting treatment; • To maintain good oral hygiene and receive routine dental check-ups during treatment; • To inform their doctor and tell their dentist that they are being treated with denosumab if they are under dental treatment or will undergo dental surgery; and • To contact their doctor and dentist immediately if they experience any problems with their mouth or teeth such as loose teeth, pain or swelling, non-healing of sores or discharge.
Target audience and planned distribution path	Target audience will be the patients. Patient reminder cards will be distributed to prescribers with instructions to provide 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 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 13: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risks		
Osteonecrosis of jaw	*Routine risk minimization measures:* • SPC Sections: 4.3, 4.4, 4.8 and 5.1 • PL Section: 2 and 4 • Recommendations for oral examination, maintenance of good oral hygiene during treatment, management of patients with unavoidable invasive dental procedure, and temporary interruption of treatment if ONJ occurs are included in Section 4.4 of SmPC. • The prescription only status of the product. *Additional risk minimisation measures*:	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* • Specific follow-up questionnaires have been proposed for Osteonecrosis of Jaw *Additional pharmacovigilance activity:* • None

	• Patient reminder card	
Atypical femoral fracture	*Routine risk minimisation measures:* • SmPC Sections 4.4 and 4.8 • PL Section: 2 and 4 • Recommendation for reporting new or unusual thigh, hip, or groin pain is included Section 4.4 of SmPC. • The prescription only status of the product *Additional risk minimisation measures*: • None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection*: • Specific follow-up questionnaires have been proposed for Atypical femoral fracture *Additional pharmacovigilance activity*: • None
Hypercalcemia several months after the last dose in patients with giant cell tumor of bone and in patients with growing skeletons	*Routine risk minimisation measures*: • SmPC Sections: 4.4 and 4.8 • PL Sections: 2 and 4 • Recommendations for monitoring the patients for signs and symptoms of hypercalcaemia after discontinuation of Jubereq treatment are included in Section 4.4 of SmPC and Section 4 of the PL • The prescription only status of the product *Additional risk minimisation measures*:	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection*: • None Additional pharmacovigilance activity: • None

	• None	
Important Potential Risks		
Cardiovascular events	*Routine risk minimisation measures*: • The prescription only status of the product *Additional risk minimisation measures*: • None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection*: • None *Additional pharmacovigilance activity*: • None
Malignancy	*Routine risk minimisation measures*: • SmPC Sections: 4.4, 4.8 and 5.1 • PL sections: 4 • Recommendations for monitoring the patients for radiological signs of malignancy, new malignancy, or osteolysis are included in Section 4.4 of SmPC. • The prescription only status of the product *Additional risk minimisation measures*: • None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* • None *Additional pharmacovigilance activity*: • None
Delay in diagnosis of primary malignancy in giant cell tumor of bone	*Routine risk minimisation measures*: • The prescription only status of the product *Additional risk minimisation*	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection*: • None

	measures: • None	*Additional pharmacovigilance activity:* • None
Hypercalcemia several months after the last dose in patients other than those with giant cell tumor of bone or growing skeletons	*Routine risk minimisation measures:* • The prescription only status of the product *Additional risk minimisation measures*: • None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection*: • None *Additional pharmacovigilance activity* • None
Missing information		
Patients with prior intravenous bisphosphonate treatment	*Routine risk minimisation measures:* • SmPC Sections: 4.5 and 5.1 • PL Section: 2 • The prescription only status of the product *Additional risk minimisation measures* • None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* • None *Additional pharmacovigilance activity:* • None
Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumor of bone	*Routine risk minimisation measures*: • The prescription only status of the product *Additional risk minimisation measures* • None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* • None *Additional pharmacovigilance activity:* • None

Off-label use in patients with giant cell tumor of bone that is resectable where resection is unlikely to result in severe morbidity	*Routine risk minimisation measures*: • The prescription only status of the product *Additional risk minimisation measures* • None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection*: • None *Additional pharmacovigilance activity:* • None
Immunogenicity following a significant change to the manufacturing process	*Routine risk communication*: • The prescription only status of the product *Additional risk minimisation measures* • None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection*: • None *Additional pharmacovigilance activity:* • None

Part VI: Summary of the risk management plan

Summary of risk management plan (RMP) for Jubereq 120 mg solution for injection (Denosumab)

This is a summary of the risk management plan (RMP) for Jubereq 120 mg solution for injection. Throughout this summary, product name to be referred as Jubereq. The RMP details important risks of Jubereq, how these risks can be minimised, and how more information will be obtained about Jubereq's risks and uncertainties (missing information).

Jubereq's summary of product characteristics (SmPC) and its package leaflet gives essential information to healthcare professionals and patients on how Jubereq should be used.
This summary of the RMP for Jubereq 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 Jubereq's RMP.

I. The medicine and what it is used for

Jubereq is indicated for the:

- Prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with advanced malignancies involving bone.
- Treatment of adults and skeletally mature adolescents with giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity.

The medicinal product contains denosumab as the active substance and it is administered via subcutaneous route.

Further information about the evaluation of Jubereq's benefits can be found in Jubereq'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 Jubereq, together with measures to minimise such risks and the proposed studies for learning more about denosumab 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 PIaddressed 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 thatthe medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (e.g. with orwithout prescription) can help to minimise its risks.

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

In the case of Jubereq, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including periodic safety update report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of denosumab is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Jubereq are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Jubereq. Potential risks are concerns forwhich 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	• Osteonecrosis of jaw (ONJ) • Atypical femoral fracture • Hypercalcemia several months after the last dose in patients with giant cell tumor of bone and in patients with growing skeletons
Important potential risks	• Cardiovascular events • Malignancy • Delay in diagnosis of primary malignancy in giant cell tumor of bone • Hypercalcemia several months after the last dose in patients other than those with giant cell tumor of bone or growing skeletons
Missing information	• Patients with prior intravenous bisphosphonate treatment • Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumor of bone • Off-label use in patients with giant cell tumor of bone that is resectable where resection is unlikely to result in severe morbidity

II.B Summary of important risks

Important Identified Risks: Osteonecrosis of jaw	
Evidence for linking the risk to the medicine	This risk was identified in randomized, controlled, phase 3 clinical trials. This risk was further supported by post-marketing reports.[1]
Risk factors and risk groups	Risk factors associated with osteonecrosis of the jaw (ONJ) include the use of antiresorptives (particularly amino bisphosphonates delivered by intravenous [IV] dosing), older age, poor dental hygiene, periodontal disease, invasive dental procedures, trauma from poorly fitting dentures, malignancy, chemotherapy (including anti-angiogenesis agents such as bevacizumab), radiation to head and neck, corticosteroids, hypercoagulable state secondary to underlying malignancy, smoking and vascular insufficiency due to thrombosis[1]
Risk minimisation measures	*Routine risk minimization measures:* • SPC Sections: 4.3, 4.4, 4.8 and 5.1 • PL Section: 2 and 4 • Recommendations for oral examination, maintenance of good oral hygiene during treatment, management of patients with unavoidable invasive dental procedure, and temporary interruption of treatment if ONJ occurs are included in Section 4.4 of SmPC. • The prescription only status of the product. *Additional risk minimisation measures:* • Patient reminder card

Important Identified Risks: Atypical femoral fracture	
Evidence for linking the risk to the medicine	This risk was identified in randomized, controlled, phase 3 clinical trials and in open-label, phase 2 clinical trials. This risk was further supported by post-marketing reports.[1]
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.[1]
Risk minimisation measures	*Routine risk minimisation measures:* • SmPC Sections 4.4 and 4.8 • PL Section: 2 and 4 • Recommendation for reporting new or unusual thigh, hip, or groin pain is included Section 4.4 of SmPC. • The prescription only status of the product *Additional risk minimisation measures:* • None
Important Identified Risks: Hypercalcemia several months after the last dose in patients with giant cell tumor of bone and in patients with growing skeletons	
Evidence for linking the risk to the medicine	This risk was identified in phase 2 clinical trials of adolescent and adult patients with giant cell tumor of bone (GCTB}, and in post-marketing reports of pediatric patients using denosumab for unauthorized indications.[1]
Risk factors and risk groups	Patients with GCTB and young patients with growing skeletons following discontinuation of denosumab. In

	general, the most common cause of hypercalcemia in humans is hyperparathyroidism, particularly among women and individuals aged 65 years or older. Hyperthyroidism and rhabdomyolysis associated with renal failure also increase the risk of hypercalcemia, as does the ingestion of large of amounts of calcium through dairy products or more recently liberal use of calcium supplements[1]
Risk minimisation measures	*Routine risk minimisation measures*: • SmPC Sections: 4.4 and 4.8 • PL Sections: 2 and 4 • Recommendations for monitoring the patients for signs and symptoms of hypercalcaemia after discontinuation of Jubereq treatment are included in Section 4.4 of SmPC and Section 4 of the PL • The prescription only status of the product *Additional risk minimisation measures*: • None
Important Potential Risk: Cardiovascular events	
Evidence for linking the risk to the medicine	The risk of cardiovascular events is a regulatory concern based on the epidemiological association between osteoprotegerin (OPG) levels and cardiovascular disease in man. Clinical data have not substantiated a cause-and-effect between OPG and atherosclerotic processes nor between denosumab or inhibition of receptor activator of nuclear factor kappa B-ligand (RANKL) and undesirable cardiovascular outcomes.[1]
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, gender, ethnicity, family history, elevated lipid levels, cigarette smoking, hypertension, diabetes, and concomitant medications, including antipsychotic agents and cyclooxygenase-2 (COX-2) inhibitors.[1]
Risk minimisation measures	*Routine risk minimisation measures*: • The prescription only status of the product *Additional risk minimisation measures*: • None
Important Potential Risks: Malignancy	
Evidence for linking the risk to the medicine	Imbalance is observed in the new primary malignancy (NPM) events between the zoledronic acid and denosumab treatment groups in the pivotal clinical studies. The results of Study 20170728, a post-marketing retrospective cohort study, showed NPM incidence rates for denosumab were generally lower than those for zoledronic acid in unadjusted analyses, suggesting no obvious excess risk associated with denosumab.[1]
Risk factors and risk groups	General factors for increasing risk of new primary malignancy include advancing age, diet, cigarette smoking, excessive ethanol consumption, and numerous environmental toxins. In addition, advanced cancer populations are at increased risk for NPM because of their existing malignancy, possible genetic predisposition, and exposure to chemotherapy and radiation treatment.[1]
Risk minimisation measures	*Routine risk minimisation measures*: • SmPC Sections: 4.4, 4.8 and 5.1 • PL sections: 4

	• Recommendations for monitoring the patients for radiological signs of malignancy, new malignancy, or osteolysis are included in Section 4.4 of SmPC. • The prescription only status of the product *Additional risk minimisation measures:* • None
Important Potential Risks: Delay in diagnosis of primary malignancy in giant cell tumor of bone	
Evidence for linking the risk to the medicine	The risk of delay in diagnosis of primary malignancy in giant cell tumor of bone is a regulatory concern based on difficulties in diagnosing primary malignancy in giant cell tumor of bone (PMGCTB). This safety concern was identified in the clinical trial setting.[1]
Risk factors and risk groups	Patients with GCTB are known to be at risk for PMGCTB.[1]
Risk minimisation measures	*Routine risk minimisation measures:* • The prescription only status of the product *Additional risk minimisation measures:* • None
Important Potential Risks: Hypercalcemia several months after the last dose in patients other than those with giant cell tumor of bone or growing skeletons	
Evidence for linking the risk to the medicine	Hypercalemia several months after the last dose in patients other than those with GCTB or growing skeletons is a theoretical concern based on the identified risk in other specific populations, GCTB, and pediatric populations.[1]
Risk factors and risk groups	Patients other than those with GCTB or growing skeletons following cessation of denosumab.[1]
Risk minimisation measures	*Routine risk minimisation measures:*

	• The prescription only status of the product *Additional risk minimisation measures:* • None
Missing information: Patients with prior intravenous bisphosphonate treatment	
Risk minimisation measures	*Routine risk minimisation measures:* • SmPC Sections: 4.5 and 5.1 • PL Section: 2 • The prescription only status of the product *Additional risk minimisation measures:* • None
Missing information: Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumor of bone	
Risk minimisation measures	*Routine risk minimisation measures*: • The prescription only status of the product *Additional risk minimisation measures:* • None
Missing information: Off-label use in patients with giant cell tumor of bone that is resectable where resection is unlikely to result in severe morbidity	
Risk minimisation measures	*Routine risk minimisation measures*: • The prescription only status of the product *Additional risk minimisationmeasures* • None
Missing information: Immunogenicity following a significant change to the manufacturing process	
Risk minimisation measures	*Routine risk communication*: • The prescription only status of the product *Additional risk minimisationmeasures*

	• 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 Jubereq 120 mg solution for injection in vial.

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

There are no studies required for Jubereq 120 mg solution for injection in vial.

Annex 4 - Specific adverse drug reaction follow-up forms

MAH has developed following targeted follow-up questionnaires for following risks:

- Osteonecrosis of jaw
- Atypical femur fracture

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 given 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; _____

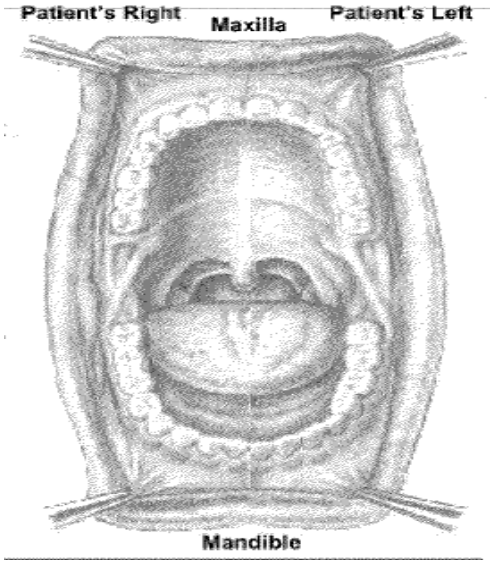
Prior history of radiation therapy to jaw:

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



Please describe location(s):

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

☐Right maxilla, medial jaw ☐Left maxilla, medial jaw

☐Right mandible teeth and lateral jaw ☐Left mandible teeth and lateral jaw

☐Right mandible, medial jaw ☐Left mandjble, medial jaw

☐Maxilla hard palate ☐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

_____

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, date of procedure_____

Dental surgery recently ☐No ☐Yes ☐Unknown; If yes, date of procedure_____

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

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

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

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

Dental abscess in affected area ☐No ☐Yes ☐Unknown

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

Osteomyelitis in affected area ☐No ☐Yes ☐Unknown

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

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

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

Dental treatment, surgery or tooth extraction to the involved area within 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

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 ☐ Unknown

REPORTER DETAILS:

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

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_____

_____

☐ 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 ☐ Unknown

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): _____

Diagnostic imagining used to confirm fracture:

☐ X-ray ☐ CT scan ☐ MRI

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 a stool, chair, first rung on a ladder or equivalent (>20 inches)

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

☐ Unknown type of trauma

Date of imaging at time of femur fracture (DD/MM/YYYY) : ___/___/_____

☐ **Please attach a copy of applicable radiology report(s)**

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 (30̊) fracture with breaking 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_____ ☐ Other _____

☐ Casting _____

☐ Surgery _____ ☐ Unknown _____

☐ Revision surgery (2nd surgery) _____

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) _____

☐ 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: State/Province: Postal code:	Email:	Tel No.

Annex 6 - Details of proposed additional risk minimisation activities

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 denosumab have access to/are provided with the following educational material:

- Patient reminder card

The patient reminder card is intended to remind patients about important safety information that they need to be aware of before and during treatment with denosumab injections for cancer-related conditions, including:

- To tell their doctor/nurse if they have any problems with their mouth or teeth before starting treatment
- To maintain good oral hygiene, receive routine dental check-ups during treatment
- To inform their doctor and tell their dentist that they are being treated with denosumab if they are under dental treatment or will undergo dental surgery
- To contact their doctor and dentist immediately if they experience any problems with their mouth or teeth such as loose teeth, pain or swelling, nonhealing of sores or discharge