SANDOZ

EU Risk Management Plan (RMP) for Denosumab 60 mg/mL, Pre-filled Syringe (Jubbonti/Rolcya)

RMP Version to be assessed as part of this application:

RMP Version number: 1.3

Data lock point for this RMP: 15-May-2025

Date of final sign off: 15-May-2025

Rationale for submitting an updated RMP: The RMP has been updated to address comments from day 36 Joint committee for medicinal products for human use and pharmacovigilance risk assessment committee assessment report.

Summary of significant changes in this RMP:

RMP part/module	High level description of major changes
Part I Product overview	Section revised to update "will the product be subject to additional monitoring in the EU" to yes.
Part VII Annexes	Annex 8: Table 'Summary of changes to the risk management plan over time' has been updated.

Other RMP versions under evaluation:

No RMP versions are currently under evaluation.

QPPV name: [redacted]

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

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List of abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
AFF	Atypical femoral fracture
ATC	Anatomical therapeutic chemical
CI	Confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
EU-Prolia/Xgeva	EU-authorized Prolia/Xgeva
GIOP	Glucocorticoid-induced osteoporosis
HALT	Hormone ablation therapy
HR	Hazard ratio
MAA	Marketing Authorization Applicant
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Male osteoporosis
ONJ	Osteonecrosis of the jaw
OPG	Osteoprotegerin
PD	Pharmacodynamics
PIL	Patient information leaflet
PIP	Pediatric Investigation Plan
PK	Pharmacokinetic
PL	Package leaflet
PMO	Postmenopausal osteoporosis
Prolia	Amgen's Prolia®; the registered trademark sign will be omitted from all following instances of Prolia in this document
PSUR	Periodic Safety Update Report
QPPV	Qualified Person for Pharmacovigilance
RANKL	Receptor activator of nuclear factor kappa-B (Ligand)
RMP	Risk Management Plan

SAE	Serious adverse event
SAF	Safety set
SC	Subcutaneous
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
SOC	System organ class
Study 101	Short key for Study CGP24112101 used in this document
Study 301	Short key for Study CGP24112301 used in this document
US-Prolia/Xgeva	US-licensed Prolia/Xgeva
Xgeva	Amgen's Xgeva®; the registered trademark sign will be omitted from all following instances of Xgeva in this document

Part I: Product(s) Overview

Table I.1 Product Overview

Active substance(s) (INN or common name)	Denosumab
Pharmacotherapeutic group(s) (ATC Code)	M05BX04
Marketing Authorization Applicant	Sandoz
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Jubbonti/Rolcya (proposed)
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class: Denosumab is a fully human monoclonal antibody of the immunoglobulin G (IgG) 2 subclass.
	Summary of mode of action: Binds to and neutralizes the activity of the human RANK ligand (RANKL). In blocking RANKL, denosumab reduces osteoclast-mediated bone resorption.
	Important information about its composition: Denosumab is a full-length human monoclonal antibody derived from the Xeno-mouseTM technology and produced in Chinese hamster ovary cells.
Hyperlink to the Product Information	[Proposed SmPC] [Proposed PI]
Indication(s) in the EEA	Current: Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures. Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. Treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture.
	Proposed: Not applicable.
Dosage in the EEA	Current: The recommended dose of Jubbonti/Rolcya is 60 mg administered as a single subcutaneous (SC) injection once every 6 months (Q6M) into the thigh, abdomen, or upper arm. Patients must be adequately supplemented with calcium and vitamin D.
	Proposed: Not applicable.
Pharmaceutical form(s) and strengths	Current: Jubbonti/Rolcya is supplied as a sterile, preservative-free solution intended for SC use (solution for injection). Jubbonti/Rolcya is provided in pre-filled syringes at a concentration of 60 mg/mL, filled to a target deliverable volume of 1.0 ml.

	Proposed: Not applicable.
Is/will the product be subject to additional monitoring in the EU?	Yes

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

As this is an application under directive article 10(4) biosimilar, modules SI is not applicable.

Part II Safety specification Module SII: Nonclinical part of the safety specification

No comparative nonclinical in vivo studies were conducted with the proposed biosimilar denosumab GP2411. This strategy is consistent with regulatory authority guidance:

- EMEA/CHMP/BMWP/42832/2005 Rev.1, Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: nonclinical and clinical issues.
- EMA/CHMP/BMWP/403543/2010, Guideline on similar biological medicinal products containing monoclonal antibodies – nonclinical and clinical issues.
- EMA/CHMP/CVMP/3Rs/677407/2015, Review and update of EMA guidelines to implement best practice with regard to 3Rs (replacement, reduction and refinement) in regulatory testing of medicinal products –report on actions taken.
- FDA guidance for industry "Scientific considerations in demonstrating biosimilarity to a reference product" (2015).
- World Health Organization (WHO). Guidelines on evaluation of biosimilars (2022).

Structural and functional characterization of denosumab syringe (GP2411), US- and EU- Prolia showed similarity between the products, all the nonclinical data generated for Prolia can be extrapolated to the biosimilar denosumab syringe, and nonclinical in vivo testing was not considered necessary to support the similarity between GP2411 and denosumab.

The findings from the originator drug (Prolia) nonclinical studies are summarized below and are considered relevant also for the biosimilar denosumab.

Table II.SII.1 Key safety findings from nonclinical studies and relevance to human usage (based on Prolia SmPC and the Canadian Product Monograph for Prolia)

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Repeated dose toxicity	Repeated dose toxicity studies were performed in cynomolgus monkeys. Consistent with the pharmacological action of denosumab, there were rapid and marked decreases in circulating markers of bone turnover at all doses. Correlating with these changes, there was increased bone mineral density observed in males and females. In addition, there was enlargement of the growth plates, decreased osteoblasts and osteoclasts, and decreased chondroclasis observed. These changes were recovered or recovering following three treatment-free months. There were no treatment related changes in opthalmoscopy, cardiovascular physiology, sperm motility and morphology, circulating immunoglobulins and lymphocyte subsets, or	Calcium levels were transiently decreased, and parathyroid levels transiently increased in ovariectomized cynomolgus monkeys treated with denosumab. Patients must be adequately supplemented with calcium and vitamin D during denosumab therapy. Hypocalcemia is a contraindication for denosumab. Special Warnings and Precautions for Use: Adequate intake of calcium and vitamin D is important in all patients. Hypocalcemia must be corrected by adequate intake of calcium and vitamin D before

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
	organ weights.	initiating therapy. Patients with severe renal impairment (creatinine clearance < 30 mL/min) or receiving dialysis are at greater risk of developing hypocalcemia. Clinical monitoring of calcium levels is recommended in patients predisposed to hypocalcemia.
Reproductive toxicity	At area under the curve (AUC) exposures up to 100-fold higher than the human exposure (Q6M), denosumab showed no evidence of impaired fertility in cynomolgus monkeys. In a study of cynomolgus monkeys dosed with denosumab during the period equivalent to the first trimester at AUC exposures up to 99-fold higher than the human dose (Q6M), there was no evidence of maternal or fetal harm. In this study, fetal lymph nodes were not examined. In cynomolgus monkeys dosed with denosumab throughout pregnancy, effects including stillbirths and increased postnatal mortality; abnormal bone growth, reduced hematopoiesis, and tooth malalignment; absence of peripheral lymph nodes; and decreased neonatal growth were noted at AUC exposures up to 119-fold higher than the human exposure (60 mg Q6M). There was no evidence of maternal harm prior to labor; adverse maternal effects occurred infrequently during labor. Maternal mammary gland development was normal. In genetically engineered mice in which RANKL has been turned off by gene removal (a "knockout mouse"), studies suggest absence of RANKL during pregnancy may interfere with maturation of the mammary gland leading to impaired lactation post-partum.	Cynomolgus monkeys exposed to denosumab in utero phenotypically resembled human infants with osteoclast-poor osteopetrosis due to inactivating mutations of RANK or RANKL. Therefore, denosumab is not recommended for use in pregnant women. Women should be advised not to become pregnant during and for at least 5 months after treatment with denosumab. It is not known if denosumab is excreted in human milk. Because denosumab has the potential to cause adverse reactions in nursing infants, a decision should be made on whether to discontinue nursing or discontinue the drug. Use in pregnant and lactating women is not considered a safety concern in this RMP. These populations are not included in the intended indications. In addition, risk minimization via product labeling to avoid pregnancy and breastfeeding is in place.
Developmental toxicity	Adolescent cynomolgus monkeys who received doses of denosumab 150 times the expected clinical exposure had enlargement of epiphyseal growth plates with decreased removal of cartilage matrix in this area, considered to be consistent with the pharmacological activity of denosumab.	Treatment with denosumab may inhibit eruption of dentition in pediatric patients and may impair bone growth in pediatric patients with open growth plates. Use in pediatric patients is not considered a safety concern in this RMP. Denosumab is not approved for use in pediatric patients. Risk minimization is in place via product labeling with respect to use in

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
		pediatric patients.

Part II Safety specification Module SIII Clinical trial exposure

This RMP is dedicated to the denosumab 60 mg/mL pre-filled syringe, which was developed as a biosimilar to the reference product Prolia with an adequate biosimilar clinical development program. Additionally, there is a separate RMP for the denosumab 120 mg/1.7 mL, single use vial with similar ingredients but with different target population and dosing as a biosimilar to Xgeva.

The tailored clinical development program comprised two studies:

- Study 301: a pivotal integrated PK, PD, confirmatory efficacy and safety study to demonstrate similarity in efficacy, but also in PK and PD between GP2411 (denosumab 60 mg/mL syringe) and EU-Prolia in 527 postmenopausal women with osteoporosis, including a subgroup switching from EU-Prolia to GP2411 (three doses at 26-week interval, total follow-up of 78 weeks).
- Study 101: a pivotal single-dose comparative PK and PD study to demonstrate PK and PD similarity between GP2411 (120 mg/1.7 mL liquid in vial), EU-Xgeva and US-Xgeva in 502 healthy male subjects (total of 39-week follow-up).

In Study 301 in postmenopausal women with osteoporosis, a total of 527 patients received at least one dose of study medication: During TP1 (up to two doses), 263 subjects were treated with GP2411 (denosumab 60 mg/mL syringe) and 264 subjects with EU-Prolia. In TP2 (week 52 to week 78), of the patients treated with GP2411, 253 subjects received a third dose. Of the subjects treated with EU-Prolia, 124 subjects were treated with one further dose of GP2411 and 125 subjects continued EU-Prolia, in TP2 (week 52 to week 78). The exposure to study drug in Study 301 is summarized in the following tables.

Table II. SIII.1 Study 301: Exposure in postmenopausal women with osteoporosis by dose (TP1 SAF)

	GP2411 (denosumab 60 mg/mL syringe)		**EU-Prolia**	
	N=263		**N=264**	
Dose	**Subjects n (%)**	**Subject-time (months)**	**Subjects n (%)**	**Subject-time (months)**
Total	263 (100)	3133.4	264 (100)	3137.6
1 dose	8 (3.0)	37.1	9 (3.4)	48.4
2 doses	255 (97.0)	3096.3	255 (96.6)	3089.2

Subject-time is the sum of each subject's treatment exposure in months, derived as (date of last visit in TP1 if no TP2 or date of first dose in TP2 – date of first dose +1)/30.25.

Table II.SIII.2 Study 301: Exposure in postmenopausal women with osteoporosis by dose (TP2 SAF)

GP2411/GP2411		EU-Prolia/EU-Prolia		EU-Prolia/GP2411	
N=253		N=125		N=124	
Subjects n (%)	Subject-time (months)	Subjects n (%)	Subject-time (months)	Subjects n (%)	Subject-time (months)
253 (100)	1537.6	125 (100)	752.6	124 (100)	752.5

Subject-time is the sum of each subject's treatment exposure in months, derived as (date of last visit – date of first dose in TP2 +1)/30.25.

GP2411: denosumab 60 mg/mL syringe

The following tables show the exposure in Study 301 by age and race.

Table II.SIII.3 Study 301: Exposure in postmenopausal women with osteoporosis by age group, during TP1 (TP1 SAF)

	GP2411 (denosumab 60 mg/mL syringe)		EU-Prolia	
	N=263		N=264	
Dose	Subjects n (%)	Subject-time (months)	Subjects n (%)	Subject-time (months)
<65 years				
Total	137 (52.1)	1634.7	139 (52.7)	1661.7
1 dose	4 (1.5)	19.2	5 (1.9)	33.8
2 doses	133 (50.6)	1615.4	134 (50.8)	1627.8
>=65 years				
Total	126 (47.9)	1498.7	125 (47.3)	1476.0
1 dose	4 (1.5)	17.9	4 (1.5)	14.6
2 doses	122 (46.4)	1480.9	121 (45.8)	1461.4

Subject-time is the sum of each subject's treatment exposure in months derived as (date of last visit in TP1 if no TP2 or first dose in TP2 - date of first dose + 1) / 30.25.

Table II.SIII.4 Study 301: Exposure in postmenopausal women with osteoporosis by age group, during TP2 (TP2 SAF)

	GP2411/GP2411		EU-Prolia/EU-Prolia		EU-Prolia/GP2411	
	N=253		N=125		N=124	
Pooled Age Group 1	**Subjects n (%)**	**Subject-time (months)**	**Subjects n (%)**	**Subject-time (months)**	**Subjects n (%)**	**Subject-time (months)**
<65 years	132 (52.2)	801.4	61 (48.8)	359.9	72 (58.1)	437.6
>=65 years	121 (47.8)	736.2	64 (51.2)	392.8	52 (41.9)	314.9

Subject-time is the sum of each subject's treatment exposure in months derived as (date of last visit - date of first dose in TP2 + 1)/ 30.25; GP2411: denosumab 60 mg/mL syringe.

Table II.SIII.5 Study 301: Exposure in postmenopausal women with osteoporosis by race during TP1 (TP1 SAF) sort by frequency

	GP2411 (denosumab 60 mg/mL syringe)		EU-Prolia	
	N=263		N=264	
Dose	**Subjects n (%)**	**Subject-time (months)**	**Subjects n (%)**	**Subject-time (months)**
White				
Total	239 (90.9)	2855.8	240 (90.9)	2846.0
1 dose	6 (2.3)	25.9	9 (3.4)	48.4
2 doses	233 (88.6)	2830.0	231 (87.5)	2797.6
Asian				
Total	23 (8.7)	265.4	24 (9.1)	291.6
1 dose	2 (0.8)	11.3	0	0
2 doses	21 (8.0)	254.1	24 (9.1)	291.6
Multiple				
Total	1 (0.4)	12.2	0	0
1 dose	0	0	0	0
2 doses	1 (0.4)	12.2	0	0

Subject-time is the sum of each subject's treatment exposure in months derived as (date of last visit in TP1 if no TP2 or first dose in TP2 - date of first dose + 1) / 30.25.

Table II.SIII.6 Study 301: Exposure in postmenopausal women with osteoporosis by race during TP2 (TP2 SAF)

	GP2411/GP2411		Prolia/Prolia		Prolia/GP2411	
	N=253		N=125		N=124	
Race (L)	Subjects n (%)	Subject-time (months)	Subjects n (%)	Subject-time (months)	Subjects n (%)	Subject-time (months)
White	231 (91.3)	1403.3	111 (88.8)	667.3	116 (93.5)	704.2
Asian	21 (8.3)	128.3	14 (11.2)	85.4	8 (6.5)	48.4
Multiple	1 (0.4)	6.0	0	0	0	0

Subject-time is the sum of each subject's treatment exposure in months derived as (date of last visit - date of first dose in TP2 + 1)/ 30.25; GP2411: denosumab 60 mg/mL syringe.

In Study 101, a total of 499 healthy subjects were treated with study medication, of which 166 subjects received GP2411. Exposure in healthy volunteers from Study 101 by race is shown in the following table.

Table II.SIII.7 Study 101: Exposure in healthy volunteers by race (SAF)

	GP2411 (Denosumab vial) N=166 n (%)	EU-Xgeva N=171 n (%)	US-Xgeva N=162 n (%)
White	163 (98.2)	167 (97.7)	161 (99.4)
Asian	1 (0.6)	2 (1.2)	0
Black or African American	1 (0.6)	1 (0.6)	1 (0.6)
Multiple	1 (0.6)	1 (0.6)	0

Part II Safety specification Module SIV: Populations not studied in clinical trials

Since this MAA has been submitted for a similar biological medicinal product under article 10(4) of Directive 2001/83/EC, as amended, a tailored clinical program was justified.

In the development of GP2411 as a similar biological medicinal product to Prolia and Xgeva, an efficacy and safety study was conducted in patients with PMO (Study 301), and a PK and PD study in healthy volunteers (Study 101).

Part II SIV.1. Exclusion criteria in pivotal clinical studies within the development program

Most exclusion criteria applied in the clinical studies with GP2411 aimed at optimization of study conduct and minimization of bias and confounding of study results and were not related to safety concerns.

In addition, as a standard precautionary measure to avoid potential harm to study subjects to the extent reasonably possible, patients with underlying diseases that might deteriorate during treatment with GP2411 were excluded from the clinical studies with GP2411.

Such underlying diseases leading to study exclusion included hypocalcemia, active infections, significant cardiovascular disorders, malignancies or patients who could develop fracture healing complications; please refer to the important risks in Section SVII.3 and/or appropriate warnings and recommendations which are included in the denosumab 60 mg/mL syringe (Jubbonti/Rolcya) SmPC

Part II SIV.2. Limitations to detect adverse reactions in clinical trial development programs

GP2411 has been developed as a biosimilar, and the safety and efficacy profile is expected to be similar to its reference product Prolia. Therefore, a limited clinical development program aimed to confirm biosimilarity, as required for all biosimilars, was performed.

Clinical trial experience with GP2411 (60 mg/mL in syringe, as biosimilar to Prolia) comprises 387 patients with postmenopausal osteoporosis (PMO) of at least 55 years of age who were treated (with GP2411) and were followed-up for up to 18 months.

In addition, GP2411 (120 mg/1.7 mL in vial, as biosimilar of Xgeva) was studied in 166 healthy volunteers that received one 35 mg dose of GP2411 and were followed-up for up to 9 months.

This clinical development program is unlikely to detect certain types of adverse reactions because they are rare adverse reactions, have a long latency, caused by prolonged exposure, or those specific to populations other than patients with PMO.

Since GP2411 showed a PK, PD efficacy and safety profile similar to that of the originator product, the established safety profile from clinical study and postmarketing experience of the originator is also applicable for the biosimilar.

Part II SIV.3. Limitations in respect to populations typically underrepresented in clinical trial development programs

Children

There is no clinical trial experience with GP2411 in children.

In line with the Pediatric Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12-Dec-2006 on medicinal products for pediatric use, GP2411, as similar biological medicinal product, is exempted from the requirement to submit a Pediatric Investigational Plan (PIP).

Prolia SmPC: The European Medicines Agency has waived the obligation to submit the results of studies with Prolia in all subsets of the pediatric population in the treatment of bone loss associated with sex hormone ablative therapy, and in subsets of the pediatric population below the age of two in the treatment of osteoporosis. See Section 4.2 of the SmPC for information on pediatric use.

There is currently an ongoing PIP for denosumab (Prolia, Xgeva) agreed upon with the EMA (EMEA-000145-PIP02-12-M04).

Elderly

Clinical trial experience in elderly subjects is available as all subjects of the 301 study population were aged ≥55 and ≤80 years at screening. Of the treated 527 subjects, 251 (47.6%) were ≥65 years at screening.

The PK properties of GP2411 and Prolia are similar as shown in the 301 study. Following the information available for the originator product, no dose adjustment is required for GP2411 in elderly (≥65 years).

Pregnant or lactating women

No clinical experience with GP2411 in pregnant or lactating women is available.

There are no adequate well-controlled studies from the use of originator product in pregnant or lactating women. According to the label, denosumab 60 mg/mL is not recommended for use in pregnant women and women of child-bearing potential not using contraception. Women should be advised not to become pregnant during and for at least 5 months after treatment with denosumab 60 mg/mL syringe.

Renal impairment

As reflected in the label, no dose adjustment is required in patients with renal impairment. No data is available in patients with severe renal impairment (GFR < 30 mL/min).

Hepatic impairment

As reflected in the label, the safety and efficacy of denosumab have not been studied in patients with hepatic impairment.

Table II.SIV.1 Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pregnant women	Not included in the clinical development program.
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program.
Population with relevant different ethnic origin	In Study 301, most patients were White. Patients of different ethnic origin were Asian.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program.
Other • Children • Elderly	Not included in the clinical development program All subjects of the 301 study population were aged ≥55 and ≤80 years at screening. Of the treated 527 subjects, 251 (47.6%) were ≥65 years at screening.

Part II Safety specification Module SV: Post-authorization experience

Not applicable for this initial submission.

Part II Module SV.1. Post-authorization exposure

Not applicable for this initial submission.

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

Potential for misuse for illegal purposes

Based on the mechanism of action of GP2411, there is no indication to suggest a potential for abuse or dependence.

Part II Safety specification Module SVII: Identified and potential risks

Part II SVII.1. Identification of safety concerns in the initial RMP submission

GP2411 was developed as a biosimilar to the reference product, Prolia. Therefore, the safety concerns of the biosimilar are expected to be the same as those for Prolia. No new safety concerns were identified in the clinical development program for GP2411.

Part II SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

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

This is the first RMP for GP2411. Hence, the risks included in this RMP are based on the originator RMP only as there is no data from the GP2411 program so far which would justify the inclusion of additional risks.

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

This is the first version of the RMP, thus there is no information pertinent to this section.

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

In the following, GP2411 safety data are presented from both studies (Study 101 and Study 301).

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

Table II.SVII.1 Important identified risk: Hypocalcemia

Potential mechanisms	Denosumab inhibits osteoclast bone resorption, thereby decreasing the release of calcium from bone into the bloodstream.
Evidence source(s) and strength of evidence	This risk was identified in phase 3, randomized, double-blind, and placebo- or active-controlled studies of the originator drug (Prolia).
Characterization of the risk:	**Frequency**: During TP1 in Study 301 there were 28 (10.6%) patients in GP2411 and 26 (9.8%) patients in the EU-Prolia arm of the study which had at least one episode of hypocalcemia. None of the subjects showed clinical symptoms associated to hypocalcemia. During TP2 only 1 (0.4%) patient had hypocalcemia in GP2411/GP2411 arm and none in the other two treatment arms. **Severity**: All cases of hypocalcemia were either grade 1 or 2. No grade 3 or more severe cases of hypocalcemia were reported during the clinical development program of GP2411. **Reversibility**: Hypocalcemia is reversible when treated with oral calcium and vitamin D supplementation. In severe cases, IV calcium supplementation may be

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

The following table shows the incidence of hypocalcemia in Study 301 during TP1.

Table II.SVII.2 Clinical trial data of GP2411: Hypocalcemia in postmenopausal women with osteoporosis (Study 301, TP1; TP1 SAF)

	GP2411 (denosumab 60 mg/mL syringe)	EU-Prolia
	N=263	N=264
	n (%)	n (%)
Number of subjects with at least one event	28 (10.6)	26 (9.8)

MedDRA version 25.0, CTCAE version 5.0, Case Retrieval Strategy Date: 03-May-2022.

The following table shows the incidence of hypocalcemia in Study 301 during TP2.

Table II.SVII.3 Clinical trial data of GP2411: Hypocalcemia in postmenopausal women with osteoporosis (Study 301, TP2; TP2 SAF)

	GP2411/GP2411	Prolia/Prolia	Prolia/GP2411
	N=253	N=125	N=124
	n (%)	n (%)	n (%)
Number of subjects with at least one event	1 (0.4)	0	0

MedDRA version 25.0, CTCAE version 5.0, Case Retrieval Strategy Date: 03-May-2022.

GP2411: denosumab 60 mg/mL syringe; Prolia: EU-Prolia.

Table II.SVII.4 Important identified Risk: Skin infection leading to hospitalization

Potential mechanisms	Keratinocytes can express RANKL and blocking RANKL in mice decreased the number of regulatory T-cells in skin, leading to an increased inflammatory response.
Evidence source(s) and strength of evidence	This risk was identified in the phase 3, randomized, double-blind, placebo- or active-controlled studies of the originator drug (Prolia).
Characterization of the risk:	**Frequency:** There were no reports of skin infection leading to hospitalization during the Study 301 **Severity:** Not applicable **Reversibility:**These events typically resolved with administration of antibiotics. **Long-term outcomes:** No long-term complications are anticipated for properly treated patients who are hospitalized due to skin infections. **Impact on quality of life:** Requires a hospital stay; patients generally recover with antibiotic treatment.
Risk factors and risk groups	Risk factors for infection in general include increasing age, immunosuppression associated with cancer, diabetes, HIV/acquired immune deficiency syndrome (AIDS), immunosuppressant drugs (e.g., corticosteroids, arthritis medications, and chemotherapy drugs), substance abuse, and malnutrition. Risk factors for skin infection in older patients include skin wounds, peripheral vascular disease, eczema/dermatitis, and venous stasis disorders.
Preventability	No preventive measures are known.
Impact on the benefit-risk balance of the product	The risk of skin infection leading to hospitalization has been considered in the product benefit-risk assessment. In light of the product labeling addressing this risk, the overall benefit-risk balance is considered to be positive.
Public health impact	Since frequency of skin infection leading to hospitalization is relatively low, absolute difference between denosumab and placebo groups, in originator's data, is relatively small, and the adverse events can be effectively treated by antibiotics, the negative impact to public health is relatively small.

GIOP = glucocorticoid-induced osteoporosis; HALT = hormone ablation therapy; PMO = postmenopausal osteoporosis; RANKL = RANK ligand.

There were no reports of skin infection leading to hospitalization in Study 301.

Table II.SVII.5 Important identified risk: Osteonecrosis of the Jaw

Potential mechanisms	Osteonecrosis of the jaw (ONJ) appears to be multifactorial and multiple hypotheses have been postulated and have included factors such as inhibition of bone 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.
Evidence source(s) and	This risk was identified in open-label long-term extensions to phase 3, randomized, double-blind, placebo-controlled studies of the originator drug

strength of evidence	(Prolia).
Characterization of the risk:	**Frequency:** No cases of ONJ have been reported during Study 101 and Study 301. **Severity:** Not applicable **Reversibility:** In general, ONJ events are clinically reversible with supportive care, antibiotics; however, surgical treatment may be required. **Long-term outcomes:** No data on long-term outcomes are available. **Impact on quality of life:** Discomfort associated with ONJ lesions and/or with more extensive treatments may impact patient wellbeing via decreased oral intake (e.g., decreased hydration and decreased nutritional intake).
Risk factors and risk groups	Risk factors include duration of exposure to denosumab, prior bisphosphonate use (particularly for extended periods of time), older age, periodontal disease, dentoalveolar surgery, trauma from poorly fitting dentures, malignancy, chemotherapy, corticosteroids, smoking, systemic or regional infection, immune-compromised state predisposing to increased risk of infection, hypercoagulable state secondary to underlying malignancy, and vascular insufficiency due to thrombosis.
Preventability	A dental examination with appropriate preventive dentistry is recommended prior to treatment with denosumab, especially in patients with risk factors. While on treatment, patients should avoid invasive dental procedures where possible. Patients who are suspected of having or who develop ONJ while on denosumab should receive care by a dentist or an oral surgeon. In patients who develop ONJ during treatment with denosumab, a temporary interruption of treatment should be considered based on individual risk/benefit assessment until the condition resolves.
Impact on the benefit-risk balance of the product	The risk of osteonecrosis of the jaw has been considered in the product benefit-risk assessment. Taking into account the product labeling and additional risk minimization activities addressing this risk, the overall benefit-risk balance is considered to be positive.
Public health impact	Significant public health impact is not expected with denosumab, as the event is rare and the actions taken to minimize the likelihood of developing ONJ are described in the prescribing information.

There were no reports of osteonecrosis of the jaw in Study 301 or Study 101.

Table II.SVII.6 Important identified risk: Hypersensitivity reactions

Potential mechanisms	Two types of allergic reactions, immunoglobulin E (lgE)- and non-lgE-mediated, appear to be related to monoclonal antibody administration. The lgE-mediated reactions can cause both wheal and flare reactions at the injection site, but may also be associated with urticaria and anaphylaxis. The mechanism of non-lgE reactions is unclear.
Evidence source(s) and strength of evidence	This risk was identified in the Prolia postmarketing setting based on a clinically and plausible association between administration of denosumab and hypersensitivity reactions.
Characterization of the risk:	**Frequency**: In study 301, no adverse drug reaction “hypersensitivity” or

	"anaphylactic reaction" has been reported. **Severity:** Not applicable. **Reversibility:** Hypersensitivity reactions are generally reversible with discontinuation of the medication, though treatment may be required. **Long-term outcomes:** No long-term complications are anticipated for properly treated hypersensitivity reactions. **Impact on quality of life:** For severe hypersensitivity reactions, patients may be treated in the emergency room and/or hospitalized for treatment. Generally, patients recover when denosumab is discontinued with or without additional treatment.
Risk factors and risk groups	Known hypersensitivity to denosumab and any of its excipients.
Preventability	No data are available on potential measures to prevent hypersensitivity reactions to denosumab. The appropriate contraindication information on hypersensitivity to denosumab and any of its excipients is included in the SmPC.
Impact on the benefit-risk balance of the product	The risk of hypersensitivity reactions has been considered in the product benefit-risk assessment. In light of the product labeling addressing this risk, the overall benefit-risk balance is considered to be positive.
Public health impact	No significant public health impact is expected as reports of severe events (e.g., anaphylaxis) are rare.

Table II.SVII.7 Important identified risk: Atypical femoral fracture

Potential mechanisms	Prolonged suppression of bone turnover may be associated with increased risk of atypical femoral fracture (AFF), but the pathogenesis remains unclear and the causes of AFF are likely multifactorial. Based on nonclinical studies, collagen cross-linking and maturation, accumulation of microdamage and advanced glycation end products, mineralization, remodeling, vascularity, and angiogenesis lend biologic plausibility to a potential association between these effects and AFF.
Evidence source(s) and strength of evidence	This risk was identified in an open-label long-term extension to phase 3, randomized, double-blind, active-controlled study.
Characterization of the risk:	**Frequency**: No subject experienced an atypical femoral fracture during clinical studies with GP2411 (Study 101 and Study 301). **Severity:** Not applicable **Reversibility:** Atypical femoral fracture is generally treatable with surgical intervention. It is unknown if the pathophysiological mechanism(s) contributing to the development of AFF are reversible after treatment is discontinued. **Long-term outcomes:** No data on long-term outcomes are available. **Impact on quality of life:** As with other femur fractures, AFF can cause short-term or long-term disability. Some data suggests that healing of AFF may be more prolonged than a typical femoral fracture.
Risk factors and risk groups	Long-term antiresorptive treatment has been associated with AFF. Corticosteroids have also been reported in the literature to potentially be associated with AFF. Atypical femoral fractures have also been reported in patients with certain comorbid conditions (e.g., vitamin D deficiency, RA,

	hypophosphatasia) and with use of bisphosphonates, glucocorticoids, and proton pump inhibitors.
Preventability	No data are currently available on potential measures to prevent AFF. Patients using long-term antiresorptives may experience pain over the femur, which requires radiological examination if atypical fracture is suspected.
Impact on the benefit-risk balance of the product	The risk of atypical femoral fracture has been considered in the product benefit-risk assessment. In light of the product labeling addressing this risk, the overall benefit-risk balance is considered to be positive.
Public health impact	Based on the infrequency of AFF in patients treated with denosumab, no significant additional public health impact is expected.

AFF = atypical femoral fracture; GIOP = glucocorticoid-induced osteoporosis; RA = rheumatoid arthritis

There were no reports of atypical femoral fracture in clinical studies with GP2411, neither in Study 101 nor in Study 301.

Table II.SVII.8 Important identified risk: Hypercalcemia in pediatric patients receiving denosumab and after treatment discontinuation

Potential mechanisms	The exact mechanism of hypercalcemia following treatment withdrawal of denosumab in the growing skeleton is not certain but may be a consequence of the following, alone, or in combination: • Hypercalcemia may result from rapid resorption of retained primary spongiosa in a skeleton with active endochondral ossification. The rate of endochondral ossification and duration of exposure to denosumab would determine the amount of accumulated primary spongiosa that could influence the magnitude of resorptive response (mechanostat-driven) and release of calcium from resorbing bone matrix via an autocrine/paracrine mechanism. • The magnitude of the resorptive response following treatment withdrawal in the immature skeleton could be dictated by the normal high rate of bone turnover in individuals with growing skeletons. • The response of the osteoclast lineage to loss of inhibition of osteoclastogenesis may be intrinsically more robust in individuals with growing skeletons.
Evidence source(s) and strength of evidence	Data to evaluate safety concern were derived from Prolia clinical trials in pediatric subjects with osteogenesis imperfecta, XGEVA clinical studies and postmarketing adverse event reporting involving pediatric patients receiving denosumab at unapproved doses and/or unapproved indications for use.
Characterization of the risk:	**Frequency:** Pediatric patients were excluded from GP2411 development program. **Severity:** Not applicable. **Reversibility:** Not applicable. **Long-term outcomes:** Not applicable. **Impact on quality of life:** Pediatric patients may present with severe hypercalcemia requiring hospitalization. Generally, patients recover when the

	hypercalcemia is treated.
Risk factors and risk groups	Pediatric patients with growing skeletons and high bone turnover disease states (such as osteogenesis Imperfecta).
Preventability	Denosumab is not indicated in pediatric patients (age < 18 years) and should not be used in pediatric patients. If used in a clinical trial setting, such as for pediatric glucocorticoid induces osteoporosis, monitoring for signs and symptoms and periodic serum calcium would be advisable.
Impact on the benefit-risk balance of the product	The benefit-risk profile of denosumab is not favorable in the pediatric patient population.
Public health impact	No significant impact on public health is anticipated as post treatment hypercalcemia attributable to denosumab has not been confirmed.

There are no study data with GP2411 on hypercalcemia in pediatric patients receiving denosumab and after treatment discontinuation.

Table II.SVII.9 Important potential risk: Fracture healing complications

Potential mechanisms	Because denosumab directly suppresses bone resorption and (indirectly) bone formation, it has the theoretical potential to delay fracture healing.
Evidence source(s) and strength of evidence	This is a theoretical risk based on the potential mechanism of action.
Characterization of the risk:	**Frequency:** No subject experienced fracture healing complications in Study 301. **Severity:** Not applicable **Reversibility:** This risk has not been substantiated; however, the effects of denosumab on osteoclasts are fully reversible. **Long-term outcomes:** This risk has not been substantiated; however, no long-term impact would be anticipated based on reversibility. **Impact on quality of life:** Fracture healing complications can cause short-term or long-term disability. Surgery may be required.
Risk factors and risk groups	General risk factors for fracture healing complications are thought to include older age, diabetes, use of medications such as non-steroidal anti-inflammatory drugs and corticosteroids, smoking, excessive alcohol use, and poor nutrition.
Preventability	No preventive measures are known.
Impact on the benefit-risk balance of the product	The potential risk of fracture healing complications has been considered in overall assessment supporting a positive benefit-risk profile.
Public health impact	No significant impact on public health is anticipated.

There were no reports of fracture healing complications in Study 301.

Table II.SVII.10 Important potential risk: Infection

Potential mechanisms	RANK ligand is expressed on activated T and B cells and in the lymph nodes and some reports have described immune modulatory effects of RANKL

	inhibition. However, no clinically relevant effect of denosumab treatment was observed on peripheral blood immune cell subset profiles in studies in healthy elderly men, postmenopausal women, and postmenopausal women with low bone mineral density (BMD). No evidence of a treatment effect of denosumab on immunoglobulin production was observed.
Evidence source(s) and strength of evidence	This is considered a potential risk based on theoretical concerns which has not been substantiated in the extensive clinical study program or in the postmarketing experience.
Characterization of the risk:	**Frequency:** In Study 301, 65 (24.7%) subjects in GP2411 arm and 77 (29.2%) subjects in EU-Prolia arm experienced infections during TP1. During TP2, 22 (8.7%) subjects in the GP2411/GP2411 arm, 27 (21.6%) subjects in the EU-Prolia/EU-Prolia arm and 17 (13.7%) in the EU-Prolia/GP2411 arm showed infections. **Severity:** Most infections reported were either graded grade 1 or grade 2. During TP1 two (0.8%) infections in the GP2411 arm and four (1.5%) infections in the EU-Prolia arm were of grade 3. No infection with grade 4 or 5 occurred in TP1. Two (0.8%) infections in each treatment arm during TP1 were classified as serious adverse events. During TP2, one infection in each treatment arm was of grade 3. No infection was reported to be grade 4 or 5. Two (1.6%) infections in the EU-Prolia/EU-Prolia arm were reported to be SAEs. In the other arms no SAEs occurred. **Reversibility:** Infections when treated appropriately are generally reversible. **Long-term outcomes:** Infection generally responds to appropriate treatment and as such no long-term effects are anticipated. **Impact on quality of life:** For severe infection, patients may be hospitalized for treatment. Generally, patients recover when their infection is treated
Risk factors and risk groups	Risk factors for infection in general include increasing age, immunosuppression associated with cancer, diabetes, HIV/AIDS, immunosuppressant drugs (e.g., corticosteroids, arthritis medications, and chemotherapy drugs), substance abuse, and malnutrition.
Preventability	No preventive measures are known.
Impact on the benefit-risk balance of the product	The potential risk of infection has been considered in overall assessment supporting a positive benefit-risk profile in the indicated populations.
Public health impact	No significant impact on public health is anticipated for this unsubstantiated risk as effective treatments are available.

The following table shows the incidence of infection in Study 301 during TP1.

Table II.SVII.11 Clinical trial data of GP2411: Infection in postmenopausal women with osteoporosis (Study 301, TP1; TP1SAF)

	GP2411 (denosumab 60 mg/mL syringe)	**EU-Prolia**
	N=263	**N=264**
	n (%)	**n (%)**
Number of subjects with at least one event	65 (24.7)	77 (29.2)

MedDRA version 25.0, CTCAE version 5.0, Case Retrieval Strategy Date: 03-May-2022.

The following table shows the incidence of infection in Study 301 during TP2.

Table II.SVII.12 Clinical trial data of GP2411: Infection in postmenopausal women with osteoporosis, (Study 301, TP2; TP2SAF)

	GP2411/GP2411	Prolia/Prolia	Prolia/GP2411
	N=253	N=125	N=124
	n (%)	n (%)	n (%)
Number of subjects with at least one event	22 (8.7)	27 (21.6)	17 (13.7)

MedDRA version 25.0, CTCAE version 5.0, Case Retrieval Strategy Date: 03-May-2022.
GP2411: denosumab 60 mg/mL syringe; Prolia: EU-Prolia.

Table II.SVII.13 Important potential risk: Cardiovascular events

Potential mechanisms	Elevated levels of osteoprotegerin (OPG) have been associated with coronary artery disease in cross-sectional studies but this association has been contradicted by preclinical and epidemiological studies demonstrating that the lack of OPG or unopposed RANKL is associated with cardiac calcification. Because of these conflicting results and because denosumab inhibits RANKL, a theoretical concern for denosumab to affect progression of atherosclerosis exists
Evidence source(s) and strength of evidence	This is a theoretical risk based on epidemiological data demonstrating elevated OPG in patients with cardiovascular disease.
Characterization of the risk:	**Frequency:** In Study 101, two subjects (1.2%) in GP2411 arm, one subject (0.6%) in EU-Xgeva and two (1.2%) subjects in US-Xgeva arm experienced cardiovascular events. In Study 301, 12 (4.6%) subjects in GP2411 arm and 7 (2.7%) subjects in EU-Prolia arm experienced cardiovascular events during TP1. During TP2, one (0.4%) subject in the GP2411/GP2411 arm and one (0.8%) subject in the EU-Prolia/EU-Prolia arm experienced cardiovascular events. In the EU-Prolia/GP2411 arm no adverse events (AEs) were reported during TP2.

	Severity: Most cardiovascular events reported were either grade 1 or grade 2. In Study 101, one event in group GP2411 was graded grade 3. No AEs with grade 4 or 5 occurred during the study. There was only one SAE reported in the course of Study 101 (in treatment group GP2411). In Study 301, during TP1 there was one fatal cardiovascular event in the GP2411 arm. All other AEs were graded either grade 1 or grade 2. Two (0.8%) cardiovascular events in GP2411 treatment arm were classified as serious adverse events. No SAEs were reported during TP1 in EU-Prolia group. During TP2, none of the cardiovascular events were graded grade 3 or higher. There was no SAE reported during TP2. **Reversibility:** This risk has not been substantiated; however, effects of denosumab to block RANKL are fully reversible. **Long-term outcomes:** This risk has not been substantiated; however, cardiovascular events could impact patient long-term outcome. **Impact on quality of life:** Cardiovascular events vary greatly in severity. For some severe events, 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 (e.g., osteoporosis, cancer) that are likely to have a higher incidence of pre-existing cardiovascular conditions and, thus, a higher incidence of cardiovascular events than that of the general population. Risk factors for atherosclerosis include age, sex, ethnicity, family history, elevated lipid levels, cigarette smoking, hypertension, diabetes, and concomitant medications, including antipsychotic agents and COX-2 inhibitors.
Preventability	No preventive measures are known.
Impact on the benefit-risk balance of the product	The potential risk of cardiovascular events has been considered in overall assessment supporting a positive benefit-risk profile in the indicated populations.
Public health impact	No significant impact on public health is anticipated for this unsubstantiated risk.

The following table shows the incidence of cardiovascular events in Study 301 during TP1.

Table II.SVII.14 Clinical trial data of GP2411: Cardiovascular events in postmenopausal women with osteoporosis (Study 301, TP1; TP1SAF)

	GP2411 (denosumab 60 mg/mL syringe)	EU-Prolia
	N=263	N=264
	n (%)	n (%)
Number of subjects with at least one event	12 (4.6)	7 (2.7)

MedDRA version 25.0, CTCAE version 5.0, Case Retrieval Strategy Date: 03-May-2022.

The following table shows the incidence of cardiovascular events in Study 301 during TP2.

Table II.SVII.15 Clinical trial data of GP2411 of cardiovascular events in postmenopausal women with osteoporosis, (Study 301, TP2; TP2SAF)

	GP2411/GP2411	Prolia/Prolia	Prolia/GP2411
	N=253	N=125	N=124
	n (%)	n (%)	n (%)
Number of subjects with at least one event	1 (0.4)	1 (0.8)	0

MedDRA version 25.0, CTCAE version 5.0, Case Retrieval Strategy Date: 03-May-2022.

GP2411: denosumab 60 mg/mL syringe; Prolia: EU-Prolia.

The following table shows the incidence of cardiovascular events in healthy volunteers in Study 101.

Table II.SVII.16 Clinical trial data of GP2411 of cardiovascular events in healthy volunteers (Study 101; SAF)

	GP2411 (vial)	EU-Xgeva	US-Xgeva
	N=166	N=171	N=162
	n (%)	n (%)	n (%)
Number of subjects with at least one event	2 (1.2)	1 (0.6)	2 (1.2)

MedDRA version 25.0, CTCAE version 5.0, Case Retrieval Strategy Date: 09-May-2022.

Table II.SVII.17 Important potential risk: Malignancy

Potential mechanisms	RANK ligand is expressed on activated T and B cells and in the lymph nodes and some reports have described immune modulatory effects of RANKL inhibition; however, in vitro studies of RANK and RANKL activity on a wide range of human tumor types provide no evidence for carcinogenic risk associated with RANKL inhibition. In in vivo rodent cancer models, RANKL inhibition has been shown to have a beneficial effect. If denosumab did affect immune function, a hypothetical association with malignancies linked to immune modulation could exist and would be expected to show the pattern of malignancy associated with immune deficiency.
Evidence source(s) and strength of evidence	This is considered a potential risk based on theoretical concerns and has not been substantiated in the extensive clinical study program or in the postmarketing experience.
Characterization of the risk:	**Frequency:** In Study 101, only one (0.6%) AE described as malignancy was reported in the EU-Xgeva arm of the trial In Study 301, 4 (1.5%) subjects in GP2411 arm and 3 (1.1%) subjects in EU-Prolia arm experienced an AE, described as malignancy, during TP1. During TP2, two (0.8%) AEs in the GP2411/GP2411 arm were reported.

	Severity: In Study 101 the only event was of grade 2 and considered serious. In TP1 of Study 301, one AE of grade 1, one AE of grade 2 and two AEs of grade 3 were observed in GP2411 arm of the trial. In the EU-Prolia arm, one AE of grade 1, one AE of grade 3 and one AE of grade 4 were observed. In each treatment arm during TP1, two SAEs were reported. During TP2 of Study 301, two AEs were reported in GP2411/GP2411 arm. Both AEs were of grade 3 and considered serious. **Reversibility:** Although some malignancies will respond to treatment, long-term survival will depend upon multiple factors and as such onset of malignancy is rarely considered reversible. **Long-term outcomes:** New primary malignancy or progression of existing malignancy may be fatal, life-threatening and long-term outcomes will likely be impacted. **Impact on quality of life:** Malignancy can be life-threatening and generally requires intervention e.g., surgery, radiation, and/or chemotherapy.
Risk factors and risk groups	General factors for risk of malignancy include advancing age, diet cigarette smoking, excessive ethanol consumption, and numerous environmental toxins. In addition, cancer populations are at increased risk for a second primary malignancy because of their existing malignancy, possible genetic predisposition, and exposure to chemotherapy and radiation treatment.
Preventability	No preventive measures are known.
Impact on the benefit-risk balance of the product	The potential risk of malignancy has been considered in overall assessment supporting a positive benefit-risk profile in the indicated populations.
Public health impact	No significant impact on public health is anticipated.

The following table shows the incidence of malignancy in Study 301 during TP1.

Table II.SVII.18 Clinical trial data of GP2411: Malignancy in postmenopausal women with osteoporosis (Study 301, TP1; TP1SAF)

	GP2411 (denosumab 60 mg/mL syringe)	EU-Prolia
	N=263	N=264
	n (%)	n (%)
Number of subjects with at least one event	4 (1.5)	3 (1.1)

MedDRA version 25.0, CTCAE version 5.0, Case Retrieval Strategy Date: 03-May-2022.

The following table shows the incidence of malignancy in Study 301 during TP2.

Table II.SVII.19 Clinical trial data of GP2411 of malignancy in postmenopausal women with osteoporosis (Study 301, TP2; TP2SAF)

	GP2411/GP2411	Prolia/Prolia	Prolia/GP2411
	N=253	N=125	N=124
	n (%)	n (%)	n (%)
Number of subjects with at least one event	2 (0.8)	0	0

MedDRA version 25.0, CTCAE version 5.0, Case Retrieval Strategy Date: 03-May-2022.
GP2411: denosumab 60 mg/mL syringe; Prolia: EU-Prolia.

The following table shows the incidence of malignancy in healthy volunteers in Study 101.

Table II.SVII.20 Clinical trial data of GP2411 of malignancy in healthy volunteers (Study 101; SAF)

	GP2411 (vial)	EU-Xgeva	US-Xgeva
	N=166	N=171	N=162
	n (%)	n (%)	n (%)
Number of subjects with at least one event	0	1 (0.6)	0

MedDRA version 25.0, CTCAE version 5.0, Case Retrieval Strategy Date: 09-May-2022.

SVII.3.2. Presentation of the missing information

Not applicable.

Part II Safety specification Module SVIII: Summary of the safety concerns

Table II.SVIII.1 Summary of safety concerns

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

Part III: Pharmacovigilance plan (including post-authorization safety studies)

Part III.1. Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond ADRs reporting and signal detection

Specific adverse reaction follow-up checklists:

Specific adverse event follow-up checklists will be used to collect further data to help further characterize and/or closely monitor each of the respective safety concerns specified below:

Table III.1 Specific adverse reaction follow-up questionnaires

Follow-up Questionnaire (Annex 4)	Safety Concern(s)	Purpose
Hypocalcemia	Hypocalcemia	To monitor the nature of hypocalcemia in patients treated with Jubbonti/Rolcya in the post-marketing environment.
Infection	Skin infection leading to hospitalization Infection	To monitor the nature of skin infections leading to hospitalization and infections of any type reported in patients treated with Jubbonti/Rolcya in the post-marketing environment.
ONJ	ONJ	To monitor the nature of ONJ in patients treated with Jubbonti/Rolcya in the post-marketing environment.
Atypical fracture	Atypical femoral fracture	To monitor the nature of AFF reported in patients treated with Jubbonti/Rolcya in the post-marketing environment.
Fracture healing	Fracture healing complications	To monitor the nature of fracture healing complications reported in patients treated with Jubbonti/Rolcya in the post-marketing environment.
Malignancy	Malignancy	To monitor the nature of malignancy adverse events reported in patients treated with Jubbonti/Rolcya in the post-marketing environment.
Hypersensitivity	Hypersensitivityreactions	To monitor the nature of hypersensitivity reported in patients treated with Jubbonti/Rolcya in the post-marketing environment.

The forms have been appended in Annex 4 of the RMP.

Part III.2. Additional pharmacovigilance activities

Not applicable as no additional pharmacovigilance activities are proposed for denosumab.

Part III.3 Summary Table of additional pharmacovigilance activities

Not applicable as no additional pharmacovigilance activities are proposed for denosumab.

Part IV: Plans for post-authorization efficacy studies

No post-authorization efficacy studies are in place or planned.

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

Risk Minimization Plan

The safety information in the proposed product information is aligned to the reference medicinal product.

Part V.1. Routine risk minimization measures

Routine risk minimization measures are aligned to the reference medicinal product.

Table V.1 Routine risk minimization activities

Safety concern	Routine risk minimization activities
Important identified risks	
Hypocalcemia	Routine risk communication: SmPC Sections 4.2 4.3, 4.4 and 4.8 Package leaflet (PL) Sections 2, 3 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: Recommendation for correction of hypocalcemia prior to initiating treatment with denosumab and clinical monitoring of calcium levels during treatment with denosumab is included in SmPC Section 4.4.
Skin infection leading to hospitalization	Routine risk communication: SmPC Sections 4.4 and 4.8 PL Sections 2 and 4 Routine risk minimization activities recommending specific clinicalmeasures to address the risk: None
Osteonecrosis of the jaw	Routine risk communication: SmPC Sections 4.4, 4.8 and 5.1 PL Sections 2 and 4 Routine risk minimization activities recommending specific clinicalmeasures to address the risk: Recommendation for oral examination, maintenance of good oral hygiene during treatment, management of patients with unavoidableinvasive dental procedures, and temporary interruption of treatment if ONJ occurs is included in SmPC Section 4.4.
Hypersensitivity reactions	Routine risk communication: SmPC Sections 4.3 and 4.8 PL Sections 2 and 4 Routine risk minimization activities recommending specific clinicalmeasures to address the risk:

Safety concern	**Routine risk minimization activities**
	None
Atypical femoral fracture	Routine risk communication: SmPC Sections 4.4, 4.8 and 5.1 PL Sections 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: Recommendation for reporting new or unusual thigh, hip, orgroin pain is included in SmPC Section 4.4.
Hypercalcemia in pediatric patients receiving denosumab and after treatment discontinuation	Routine risk communication: SmPC Sections 4.2, 4.4, 4.8 and 5.1 Routine risk minimization activities recommending specific clinicalmeasures to address the risk: None
Important potential risks	
Fracture healing complications	Routine risk communication: None Routine risk minimization activities recommending specific clinicalmeasures to address the risk: None
Infection	Routine risk communication: SmPC Section 4.8 PL Section 4 Routine risk minimization activities recommending specific clinicalmeasures to address the risk: None
Cardiovascular events	Routine risk communication: None Routine risk minimization activities recommending specific clinicalmeasures to address the risk: None
Malignancy	Routine risk communication: None Routine risk minimization activities recommending specific clinicalmeasures to address the risk: None
Missing information	
None	

Part V.2. Additional Risk minimization measures

Osteonecrosis of the Jaw is the only risk requiring additional risk minimization measures; this in order to prevent the occurrence of this risk.

Patient Reminder Card for Osteonecrosis of the Jaw (ONJ)

Objectives:

Patient reminder cards will be provided to address the following risk: Osteonecrosis of the jaw

Rationale for the additional risk minimization activity:

The purpose of the patient reminder card is to remind patients about important safety information that they need to be aware of before and during treatment with GP2411 for osteoporosis and bone loss, including:

- the risk of osteonecrosis of the jaw during treatment with GP2411;
- the need to highlight any problems with their mouth or teeth to their doctors/nurses before starting treatment;
- the need to ensure good oral hygiene during treatment;
- the need to inform their dentist of treatment with GP2411 and to contact their doctor or dentist if problems with the mouth or teeth occur during treatment.

Target audience and planned distribution path:

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

The methods for dissemination and the target audience in each Member State are determined at national level by the respective competent authority of the Member State.

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

Routine pharmacovigilance activities will be performed to identify new safety signals and monitor reporting trends.

The key safety messages for patient reminder card can be found in Annex 6.

Part V.3. Summary of risk minimization measures

Table V.3 Summary of pharmacovigilance activities and risk minimization activities by safety concerns

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important identified risks		
Hypocalcemia	Routine risk minimization measures: • SmPC Section 4.4, where recommendation regarding correction and monitoring of calcium levels is provided • SmPC Sections 4.2, 4.3, 4.4 and 4.8 • PL Sections 2, 3 and 4 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Adverse reaction follow-up questionnaire Additional pharmacovigilance activities: • None
Skin infection leading to hospitalization	Routine risk minimization measures: • SmPC Sections 4.4 and 4.8 • PL Sections 2 and 4 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Adverse reaction follow-up questionnaire Additional pharmacovigilance activities: • None
Osteonecrosis of the jaw	Routine risk minimization measures: • SmPC Section 4.4, where oral hygiene and dental management guidance is provided • SmPC Sections 4.4, 4.8 and 5.1 • PL Sections 2 and 4 Additional risk minimization measures: • Patient reminder card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Adverse reaction follow-up questionnaire Additional pharmacovigilance activities: • None
Hypersensitivity reactions	Routine risk minimization measures: • SmPC Sections 4.3 and 4.8 • PL Sections 2 and 4 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Adverse reaction follow-up questionnaire Additional pharmacovigilance activities: • None
Atypical femoral fracture	Routine risk minimization measures: • SmPC Section 4.4, where recommendation for reporting potential symptoms is provided	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Adverse reaction follow-up questionnaire Additional pharmacovigilance activities:

Safety concern	Risk minimization measures	Pharmacovigilance activities
	• SmPC Sections 4.4, 4.8 and 5.1 • PL Sections 2 and 4 Additional risk minimization measures: • None	• None
Hypercalcemia in pediatric patients receiving denosumab and after treatment discontinuation	Routine risk minimization measures: • SmPC Sections 4.2, 4.4, 4.8 and 5.1 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Important potential risks		
Fracture healing complications	Routine risk minimization measures: • None Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Adverse reaction follow-up questionnaire Additional pharmacovigilance activities: • None
Infection	Routine risk minimization measures: • SmPC Section 4.8 • PL Section 4 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Adverse reaction follow-up questionnaire Additional pharmacovigilance activities: • None
Cardiovascular events	Routine risk minimization measures: • None Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Malignancy	Routine risk minimization measures: • None Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Adverse reaction follow-up questionnaire Additional pharmacovigilance activities: • None
Missing information		
None		

Part VI: Summary of the risk management plan for Jubbonti/Rolcya

This is a summary of the risk management plan (RMP) for Jubbonti/Rolcya (denosumab 60 mg/mL syringe), a biosimilar to Prolia®. The RMP details important risks of Jubbonti/Rolcya, how these risks can be minimized and how more information will be obtained about Jubbonti's/Rolcya risks and uncertainties (missing information).

Jubbonti's/Rolcya summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how Jubbonti/Rolcya should be used.

This summary of the RMP for Jubbonti/Rolcya should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of 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 Jubbonti's/Rolcya RMP.

Part VI: I. The medicine and what it is used for

Jubbonti/Rolcya is authorized for the treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures, the treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures, and treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture (see SmPC for the full indication). It contains denosumab as the active substance and it is given by subcutaneous injection.

Further information about the evaluation of Jubbonti/Rolcya benefits can be found in Jubbonti's/Rolcya EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage: https://www.ema.europa.eu/medicines/human/EPAR/jubbonti.

Part VI: II. Risks associated with the medicine and activities to minimize or further characterize the risks

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

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

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

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

In the case of Jubbonti/Rolcya, these measures are supplemented with *additional risk minimization measures* mentioned under relevant important risks, below.

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

Part VI – II.A: List of important risks and missing information

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

Table VI.II.1 List of important risks and missing information

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

Part VI – II.B: Summary of important risks

The safety information in the proposed product information is aligned to the reference medicinal product.

Table VI.II.2 Important identified risk: Hypocalcemia

Evidence for linking the risk to the medicine	This risk was identified in the phase 3, randomized, double-blind, placebo- or active-controlled studies with originator drug (Prolia).

Risk factors and risk groups	Risk factors include severe renal impairment and hyperphosphatemia. Other risks factors may include a history of hypoparathyroidism, parathyroid hormone resistance, vitamin D deficiency or resistance, thyroid surgery, parathyroid surgery, malabsorption syndromes, excision of small intestine, severe renal impairment (creatinine clearance < 30 mL/min), dialysis, and some medications.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4, where recommendation regarding correction and monitoring of calcium levels is provided • SmPC Sections 4.2, 4.3, 4.4 and 4.8 • PL Sections 2, 3 and 4 Additional risk minimization measures: • None

Table VI.II.3 Important identified risk: Skin infection leading to hospitalization

Evidence for linking the risk to the medicine	This risk was identified in the phase 3, randomized, double-blind, placebo- or active-controlled studies with originator drug (Prolia).
Risk factors and risk groups	Risk factors for infection in general include increasing age, immunosuppression associated with cancer, diabetes, human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), immunosuppressant drugs (e.g., corticosteroids, arthritis medications, and chemotherapy drugs), substance abuse, and malnutrition. Risk factors for skin infection in older patients include skin wounds, peripheral vascular disease, eczema/dermatitis, and venous stasis disorders.
Risk minimization measures	Routine risk minimization measures: • SmPC Sections 4.4, and 4.8 • PL Sections 2 and 4 Additional risk minimization measures: • None

Table VI.II.4 Important identified risk: Osteonecrosis of the jaw

Evidence for linking the risk to the medicine	This risk was identified in open-label long-term extensions to phase 3, randomized, double-blind, placebo-controlled studies with originator drug (Prolia).
Risk factors and risk groups	Risk factors include duration of exposure to denosumab, prior bisphosphonate use (particularly for extended periods of time), older age, periodontal disease, dentoalveolar surgery, trauma from poorly fitting dentures, malignancy, chemotherapy, corticosteroids, smoking, systemic or regional infection, immune-compromised state predisposing to increased risk of infection, hypercoagulable state secondary to underlying malignancy, and vascular

	insufficiency due to thrombosis.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4, where oral hygiene and dental management guidance is provided • SmPC Sections 4.4, 4.8 and 5.1 • PL Sections 2 and 4 Additional risk minimization measures: • Patient reminder card

Table VI.II.5 Important identified risk: Hypersensitivity reactions

Evidence for linking the risk to the medicine	This risk was identified in the postmarketing setting based on a clinically plausible association between administration of denosumab and hypersensitivity reactions with originator drug (Prolia).
Risk factors and risk groups	Known hypersensitivity to denosumab and any of its excipients.
Risk minimization measures	Routine risk minimization measures: • SmPC Sections 4.3 and 4.8 • PL Sections 2 and 4 Additional risk minimization measures: • None

Table VI.II.6 Important identified risk: Atypical femoral fracture

Evidence for linking the risk to the medicine	This risk was identified in an open-label long-term extension to a phase 3, randomized, double-blind, active-controlled study with originator drug (Prolia).
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 (e.g., vitamin D deficiency, rheumatoid arthritis, hypophosphatasia) and with use of bisphosphonates, glucocorticoids, and proton pump inhibitors.
Risk minimization measures	Routine risk minimization measures: SmPC Section 4.4, where recommendation for reporting potential symptoms is provided • SmPC Sections 4.4, 4.8 and 5.1 • PL Sections 2 and 4 Additional risk minimization measures: • None

Table VI.II.7 Important identified risk: Hypercalcemia in pediatric patients receiving denosumab and after treatment discontinuation

Evidence for linking the risk to the medicine	Data to evaluate safety concerns were derived from Prolia clinical studies in pediatric subjects with osteogenesis imperfecta, XGEVA clinical studies and postmarketing adverse event reporting involving pediatric patients receiving denosumab at unapproved doses and/or unapproved indications for use.
Risk factors and risk groups	Pediatric patients with growing skeletons and high bone turnover disease states (such as osteogenesis Imperfecta).
Risk minimization measures	Routine risk minimization measures: • SmPC Sections 4.2, 4.4, 4.8 and 5.1 Additional risk minimization measures: • None

Table VI.II.8 Important potential risk: Fracture healing complications

Evidence for linking the risk to the medicine	This is a theoretical risk based on the potential mechanism of action with denosumab.
Risk factors and risk groups	General risk factors for fracture healing complications are thought to include older age, diabetes, use of medications such as non-steroidal anti-inflammatory drugs and corticosteroids, smoking, excessive alcohol use, and poor nutrition.
Risk minimization measures	Routine risk minimization measures: • None Additional risk minimization measures: • None

Table VI.II.9 Important potential risk: Infection

Evidence for linking the risk to the medicine	This is considered a potential risk based on theoretical concerns which has not been substantiated in the extensive clinical study program or in the postmarketing experience of Prolia.
Risk factors and risk groups	Risk factors for infection in general include increasing age, immunosuppression associated with cancer, diabetes, HIV/AIDS, immunosuppressant drugs (e.g., corticosteroids, arthritis medications, and chemotherapy drugs), substance abuse, and malnutrition.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.8 • PL Section 4 Additional risk minimization measures:

	• None

Table VI.II.10 Important potential risk: Cardiovascular events

Evidence for linking the risk to the medicine	This is a theoretical risk based on epidemiological data demonstrating elevated osteoprotegerin in patients with cardiovascular disease of Prolia.
Risk factors and risk groups	The denosumab development program comprised studies of older subject populations (e.g., osteoporosis, cancer) that are likely to have a higher incidence of pre-existing cardiovascular conditions and, thus, a higher incidence of cardiovascular toxicities than that of the general population. Risk factors for atherosclerosis include age, sex, ethnicity, family history, elevated lipid levels, cigarette smoking, hypertension, diabetes, and concomitant medications, including antipsychotic agents and COX-2 inhibitors.
Risk minimization measures	Routine risk minimization measures: • None Additional risk minimization measures: • None

Table VI.II.11 Important potential risk: Malignancy

Evidence for linking the risk to the medicine	This is considered a potential risk based on theoretical concerns and has not been substantiated in the extensive clinical study program or in the postmarketing experience with Prolia.
Risk factors and risk groups	General factors for risk of malignancy include advancing age, diet, cigarette smoking, excessive ethanol consumption, and numerous environmental toxins. In addition, cancer populations are at increased risk for a second primary malignancy because of their existing malignancy, possible genetic predisposition, and exposure to chemotherapy and radiation treatment.
Risk minimization measures	Routine risk minimization measures: • None Additional risk minimization measures: • None

Part VI – II.C: Post-authorization development plan

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

There are no studies which are conditions of the marketing authorization or specific obligation of Jubbonti/Rolcya.

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

There are no studies required for Jubbonti/Rolcya.

Part VII: Annexes

Annex 4 – Specific adverse drug reaction follow-up forms

- Annex 4.1 Follow-up form: Hypocalcemia
  (Version 1.0/Dec-2021)
- Annex 4.2 Follow-up form: Infection
  (Version 1.0/Dec-2021)
- Annex 4.3 Follow-up form: ONJ
  (Version 1.0/Dec-2021)
- Annex 4.4 Follow-up form: Atypical fractures
  (Version 1.0/Dec-2021)
- Annex 4.5 Follow-up form: Fracture healing
  (Version 1.0/Dec-2021)
- Annex 4.6 Follow-up form: Malignancy
  (Version 1.0/Dec-2021)
- Annex 4.7 Follow-up form: Hypersensitivity
  (Version 1.0/Dec-2021)

Annex 4.1 – Follow-up form: Hypocalcemia

(Version 1.0/Dec-2021)

Annex 4.2 – Follow-up form: Infection

(Version 1.0/Dec-2021)

Annex 4.3 – Follow-up form: ONJ

(Version 1.0/Dec-2021)

Annex 4.4 – Follow-up form: Atypical fractures

(Version 1.0/Dec-2021)

Annex 4.5 – Follow-up form: Fracture healing

(Version 1.0/Dec-2021)

Annex 4.6 – Follow-up form: Malignancy

(Version 1.0/Dec-2021)

Annex 4.7 – Follow-up form: Hypersensitivity

(Version 1.0/Dec-2021)

Annex 6 – Details of proposed additional risk minimization activities

Prior to the launch of denosumab in each Member State the Marketing Authorization Holder (MAH) must agree about the content and format of the educational program, including communication media, distribution modalities, and any other aspects of the program, with the National Competent Authority.

The MAH shall ensure that in each Member State where denosumab is marketed, all healthcare professionals and patients/carers who are expected to prescribe and dispense denosumab have access to/are provided with the following educational package to be disseminated through professional bodies:

The Summary of Product Characteristics

Patient Reminder Card

Key messages of Patient Reminder Card:

- Patient reminder cards for osteonecrosis of the jaw (ONJ) will be distributed to prescribers for denosumab with background information of the purpose of the patient reminder card and instructions to provide it to patients.
- The patient reminder card will remind patients about important safety information that they need to be aware of before and during treatment with denosumab injections for osteonecrosis and bone loss, including:
  - The risk of osteonecrosis of the jaw during treatment with denosumab.
  - The need to highlight any problems with their mouth or teeth to their doctors/nurses before starting treatment.
  - The need to ensure good oral hygiene during treatment.
  - The need to inform their dentist of treatment with denosumab and to contact their doctor or dentist if problems with the mouth or teeth occur during treatment.

The patient reminder card will be distributed by mail and prescribers will be provided with contact details to request additional copies of the card.