EU Risk Management Plan (RMP) for Xbryk (Denosumab)

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QPPV name: John Hart

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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

ATC	Anatomical Therapeutic Chemical Classification
AUC	Area Under The Plasma Concentration-Time Curve
DNA	Deoxyribonucleic Acid
EC	European Commission
eCTD	Electronic Common Technical Document
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
IgG2	Immunoglobulin G2
INN	International Non-Proprietary Name
MAH	Marketing Authorisation Holder
max	Maximum
min	Minimum
OPG	Osteoprotegerin
OPG-Fc	Osteoprotegerin Bound To Fragment Crystallisable
PFS	Pre-Filled Syringe
PL	Package Leaflet
PSUR	Periodic Safety Update Report
QPPV	Qualified Person Responsible For Pharmacovigilance
RANK	Receptor Activator Of Nuclear Factor Kβ
RANKL	Receptor Activator Of Nuclear Factor Kβ Ligand
RMP	Risk Management Plan
SD	Standard Deviation
SmPC	Summary Of Product Characteristics
TNF	Tumour Necrosis Factor
TRAIL	Tumour Necrosis Factor-Related Apoptosis Inducing Ligand
US	United States

Part I: Product(s) overview

Table Part I.1: Product(s) overview

Active substance(s) (INN or common name)	Denosumab
Pharmacotherapeutic group(s) (ATC Code)	Drugs for treatment of bone diseases – other drugs affecting bone structure and mineralisation (M05BX04)
Marketing Authorisation Applicant	Samsung Bioepis NL B.V. (the Netherlands)
Medicinal products to which this RMP refers	1
Invented name(s) in the EEA	Xbryk
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class:** Denosumab is a fully human monoclonal IgG2 antibody against the receptor activator of nuclear factor κB (RANK) ligand (RANKL).
	Summary of mode of action: Denosumab targets and binds with high affinity and specificity to RANKL, a transmembrane or soluble protein essential for the formation, function, and survival of osteoclasts. Osteoclasts are the sole cell type responsible for bone resorption. Increased osteoclast activity, stimulated by RANKL, is a key mediator of bone destruction in metastatic bone disease and multiple myeloma. By binding to RANKL, denosumab prevents the RANKL/RANK interaction from occurring and resulting in reduced osteoclast numbers and function, thereby decreasing bone resorption and cancer-induced bone destruction. Giant cell tumours of the bone are characterised by neoplastic stromal cells expressing RANKL and osteoclast-like giant cells expressing RANK. In patients with giant cell tumour of the bone, denosumab binds to RANKL, significantly reducing or eliminating osteoclast-like giant cells. Consequently, osteolysis is reduced and the proliferative tumour stroma is replaced with a non-proliferative, differentiated, densely woven new bone.

Table Part I.1: Product(s) overview

	Important information about its composition: Denosumab is produced in Chinese hamster ovary cells by recombinant DNA technology.
Hyperlink to the Product Information	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:** Prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) 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. 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 recommended dose 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.
Pharmaceutical form(s) and strengths	**Current:** Solution for injection in a vial Each vial contains 120 mg of denosumab in approximately 1.7 mL of solution (70 mg/mL).
Is/will the product be subject to additional monitoring in the EU?	Yes

ATC = anatomical therapeutic chemical classification; DNA = deoxyribonucleic acid; EEA = European Economic Area; EU = European Union; IgG2 = immunoglobulin G2; INN = international non-proprietary name.

Part II: Safety specification

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

Based on the Guideline on good pharmacovigilance practices Module V – Risk management systems (Rev. 2), this module is not applicable for the medicinal product(s) seeking a marketing authorisation according to Article 10(4) of Directive 2001/83/EC, as amended.

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

Samsung Bioepis developed XBRYK as a proposed biosimilar medicinal product to the reference product XGEVA (denosumab).

A series of *in-vitro* pharmacodynamics studies were performed in order to demonstrate the similarity between XBRYK (denosumab biosimilar) and XGEVA. *In vivo* non-clinical studies for XBRYK were not required, since the data from the comparative structural analyses, physicochemical analyses, as well as *in vitro* non-clinical studies and functional assays demonstrated the similarity between XBRYK and XGEVA.

In addition, no safety pharmacology, genotoxicity, carcinogenicity, reproductive and development toxicity, local tolerance, or other toxicity studies were conducted fully in line with the European Medicines Agency (EMA) guideline EMA/CHMP/BMWP/42832/2005 Rev 1.

A detailed description of the non-clinical development programme for XBRYK is provided in the eCTD Module 2.4 (Non-clinical Overview).

Since the overall non-clinical programme for XBRYK showed that the toxicity profile of XBRYK was similar to that of the reference product XGEVA, the key non-clinical safety findings in Table SII.1 are based on the data collected for the reference product XGEVA.

Table SII.1: Key safety findings from non-clinical studies and relevance to human use

Key safety findings	Relevance to human usage
Transient decrease in calcium levels Calcium levels were transiently decreased and parathyroid hormone levels transiently increased in ovariectomised monkeys treated with denosumab [1].	Hypocalcaemia is a known and common risk associated with denosumab use, and denosumab is contraindicated in patients with severe, untreated hypocalcaemia. However, hypocalcaemia does not represent an important risk of denosumab in the context of its use for prevention of skeletal related events in adults with advanced malignancies involving bone and treatment of giant cell tumour of bone.
Delayed callus remodelling Denosumab was found to delay callus remodelling in human RANKL knock-in mouse animal model, though callus strength and stiffness were greater in treated animals than in controls [2]. There was no effect of denosumab on fracture union or initial callus formation in this animal model.	Fracture healing complications represent a theoretical, important potential risk of denosumab when used in 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

Key safety findings	Relevance to human usage
	treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture. However, fracture healing complications do not represent an important risk of denosumab in the context of its use for prevention of skeletal related events in adults with advanced malignancies involving bone and treatment of giant cell tumour of bone.
Immunogenicity Denosumab was highly immunogenic in 1-, 6-, and 12-month studies in cynomolgus monkeys [1].	The relevance of this finding to human use cannot be drawn from the non-clinical data. While a high prevalence of binding and/or neutralising antibodies was seen at all doses in cynomolgus monkeys treated with denosumab, no corresponding production of antibodies was seen in humans. In clinical studies with denosumab, neutralising antibodies to denosumab have not been detected and less than 1% of the subjects treated with denosumab for up to 5 years developed non-neutralising binding antibodies, which were mostly transient, with no evidence of altered pharmacokinetics, toxicity, or clinical response [1].

Key safety findings	Relevance to human usage
Reproductive and developmental toxicity Denosumab is a potent inhibitor of RANKL. In non-clinical studies conducted in knock-out mice lacking RANK or RANKL, impairment of lymph node formation was observed in the foetus [3]. An absence of lactation due to inhibition of mammary gland maturation (lobuloalveolar gland development during pregnancy) was also observed in knock-out mice lacking RANK or RANKL [4, 5]. Absence of osteoclasts and bone resorption in RANK/RANKL knock-out mice during skeletal development results in osteopetrosis and failure of tooth eruption [6, 7]. In neonatal pre-weaning rats, inhibition of RANKL with high doses of a construct of OPG-Fc was associated with inhibition of bone growth and tooth eruption [1].	The use of denosumab during pregnancy is not recommended. It is unknown whether denosumab is excreted in human milk. A decision on whether to abstain from breast-feeding or to abstain from therapy with denosumab should be made, considering the benefit of breastfeeding to the newborn/infant and the benefit of denosumab therapy to the woman. The safety of denosumab has not been established in the paediatric population other than skeletally mature paediatric patients with giant cell tumour of bone. Denosumab should not be used in paediatric population because of safety concerns of serious hypercalcaemia, potential inhibition of bone growth, and lack of tooth eruption.
Denosumab had no effect on male or female fertility [1]. At AUC exposures up to 100-fold higher than the human exposure (60 mg every 6 months), denosumab showed no evidence of impaired fertility in cynomolgus monkeys [8].	There are no data on the effect of denosumab on human fertility.
In a embryo-foetal development study in 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 (60 mg every 6 months), there was no evidence of maternal or foetal harm. In this study, foetal lymph nodes were not examined [8]. In a pre-postnatal development study in cynomolgus monkeys dosed with denosumab throughout pregnancy at AUC exposures 119-fold higher than the human dose (60 mg every 6 months), there were increased stillbirths and postnatal mortality; abnormal bone growth resulting in reduced bone strength, reduced haematopoiesis, and tooth malalignment, absence of peripheral	Denosumab is not intended to be used in the paediatric population other than in skeletally mature adolescents with giant cell tumour of bone, because of concerns of serious hypercalcaemia, potential inhibition of bone growth, and lack of tooth eruption. Molar tooth eruption in rats and humans is considered to share similar mechanisms. Molar eruption is often inhibited in osteopetrotic humans with impaired osteoclast activity and delayed tooth eruption has been reported in children with osteogenesis imperfecta treated with bisphosphonates [8]. With respect to safety of denosumab in adolescent girls, human mammary gland

Key safety findings	Relevance to human usage
lymph nodes; and decreased neonatal growth [8]. A no observed adverse effect level for reproductive effects was not established. There was no evidence of maternal harm prior to labour; adverse maternal effects occurred infrequently during labour. Maternal mammary gland development was normal [8]. Following a 6-month period after birth, bone related changes showed recovery and there was no effect on tooth eruption. However, the effects on lymph nodes and tooth malalignment persisted, and minimal to moderate mineralisation in multiple tissues was seen in one animal (relation to treatment uncertain) [8]. In neonatal cynomolgus monkeys exposed in utero to denosumab at 50 mg/kg, there was increased postnatal mortality, osteopetrosis and reduced haematopoiesis, absence of peripheral lymph nodes, and decreased neonatal growth [8]. In general, the effects observed in mothers and infants were consistent with the pharmacological action of denosumab and similar to those seen in RANKL-deficient humans. Thus, denosumab given early in pregnancy did not cause maternal or foetal harm, however, denosumab given throughout pregnancy did have an impact on the mother at delivery, the foetus in late gestation, and on the viability of the infant [8]. Adolescent primates dosed with denosumab at 27 and 150 times (10 and 50 mg/kg dose) the clinical exposure had abnormal growth plates [1]. In nonhuman primates dosed for 1 year with up to 50 mg/kg of denosumab, no changes in adolescent mammary tissue were observed [8].	development would be expected to resemble that of the nonhuman primate. Based on the lack of findings in multiple nonhuman primate studies, effects on development of the lactating mammary tissue are not anticipated to be a significant issue. Further, since denosumab clears from the circulation, it is not anticipated that there will be long-term consequences in mammary gland development [8].

Key safety findings	Relevance to human usage
Carcinogenicity No carcinogenicity studies were conducted in accordance with available regulatory guidance. Ovariectomised monkeys treated for up to 16 months with denosumab showed no evidence of pre-neoplastic lesions. However, potential to interfere with the immune system cannot be discounted [1].	The multiple signalling pathways involved in OPG effects, and by analogy possibly also relevant in the case of denosumab, indicate a potential for dysregulation of functions that could be critical in e.g., cancer pathogenesis. Malignancy represents an important potential risk of denosumab (refer to Part II: Module SVII).

AUC = area under the plasma concentration-time curve; OPG = osteoprotegerin; OPG-Fc = osteoprotegerin bound to fragment crystallisable; RANK = receptor activator of nuclear factor κB; RANKL = receptor activator of nuclear factor κB ligand.

Part II: Module SIII - Clinical trial exposure

The clinical development programme for denosumab 60 mg pre-filed syringe (PFS) (hereinafter referred to as OBODENCE) consists of a completed Phase I study in healthy male subjects (SB16-1001) and a completed Phase III study in postmenopausal women with osteoporosis (SB16-3001).

These studies were conducted with the reference product PROLIA, a medicinal product containing the same active ingredient as XGEVA and formulated as PFS containing 60 mg of denosumab in 1 mL of solution (60 mg/mL). PROLIA is approved for the 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, and treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture [9]. The studies established biosimilarity between OBODENCE and PROLIA, and no biosimilarity studies were deemed necessary using XBRYK and XGEVA (120 mg of denosumab at 70 mg/mL).

Study SB16-1001 was a randomised, double-blind, three-arm, parallel group, single-dose study to compare the pharmacokinetics, pharmacodynamics, safety, tolerability, and immunogenicity between OBODENCE and PROLIA (EU and United States [US] sourced) in healthy male subjects.

Study SB16-3001 was a randomised, double-blind, multicentre study to evaluate the efficacy, safety, tolerability, pharmacokinetics, pharmacodynamics, and immunogenicity of OBODENCE compared to PROLIA (EU sourced) in postmenopausal women with osteoporosis.

The subject exposure to OBODENCE and PROLIA, including the treatment duration, in study SB16-3001 is provided in Table SIII.1, while the subject demographic characteristics are detailed in Table SIII.2 (for study SB16-1001) and Table SIII.3 (for study SB16-3001).

A detailed description of the clinical development programme for XBRYK is provided in the eCTD Module 2.5 (Clinical Overview) and Module 2.7.4 (Summary of Clinical Safety).

The safety profile of denosumab and its positive benefit-risk balance is based solely on the data collected for the reference product XGEVA [10, 11], taking into account data collected in studies SB16-1001 and SB16-3001.

Table SIII.1: Summary of exposure to investigational product in study SB16-3001 (Safety Set 1)

Exposure	OBODENCE (N = 225)	PROLIA			Total (N = 456)[b]
		Overall (N = 231)	OBODENCE (N = 100)[a]	PROLIA (N = 101)[a]	
Number of IP administration, n (%)					
1 injection	9 (4.0)	20 (8.7)	-	-	29 (6.4)
2 injections	10 (4.4)	10 (4.3)	-	-	20 (4.4)
3 injections	206 (91.6)	201 (87.0)	100 (100.0)	101 (100.0)	407 (89.3)
Duration of exposure to IP (days) in Main period (up to Month 12)					
n	225	231	-	-	456
Mean (SD)	351.8 (45.74)	338.2 (74.50)	-	-	344.9 (62.31)
Median	359.0	359.0	-	-	359.0

Exposure	OBODENCE (N = 225)	PROLIA			Total (N = 456)[b]
		Overall (N = 231)	OBODENCE (N = 100)[a]	PROLIA (N = 101)[a]	
Min, max	16, 372	6, 372	-	-	6, 372
Duration of exposure to IP (days) in Overall study period (up to Month 18)					
n	225	231	100	101	456
Mean (SD)	518.5 (88.04)	496.4 (129.03)	543.4 (3.99)	542.9 (4.29)	507.3 (111.15)
Median	541.0	541.0	542.0	541.0	541.0
Min, max	16, 553	6, 561	540, 561	523, 554	6, 561

IP = investigational product; max = maximum; min = minimum; SD = standard deviation.; PFS = pre-filled syringe.

[a] Based on subjects in the Safety Set 2, PROLIA+OBODENCE and PROLIA+PROLIA may not add up to PROLIA Overall.

[b] Among 457 randomised subjects, one subject did not receive the investigational product. Therefore, 456 subjects were evaluated in Safety Set 1

Note: Percentages were based on the number of patients in the Safety Set 1.

Table SIII.2: Demographic characteristics of subjects in study SB16-1001 (Randomised Set)

Characteristics	OBODENCE (N = 56)	PROLIA (EU sourced) (N = 56)	PROLIA (US sourced) (N = 56)	Total (N = 168)
Age (years)				
Mean (SD)	39.1 (7.71)	40.2 (8.13)	40.8 (7.88)	40.0 (7.89)
Median	39.5	40.5	41.0	41.0
Min, max	28, 55	28, 55	28, 55	28, 55
Sex, n (%)				
Male	56 (100.0)	56 (100.0)	56 (100.0)	56 (100.0)
Race, n (%)				
White	38 (67.9)	36 (64.3)	41 (73.2)	115 (68.5)
Black or African American	17 (30.4)	17 (30.4)	12 (21.4)	46 (27.4)
Asian	1 (1.8)	3 (5.4)	3 (5.4)	7 (4.2)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Multiple	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity, n (%)				
Hispanic or Latino	10 (17.9)	9 (16.1)	4 (7.1)	23 (13.7)
Not Hispanic or Latino	46 (82.1)	47 (83.9)	52 (92.9)	145 (86.3)

EU = European Union; max = maximum; min = minimum; SD = standard deviation; US = United States.
Note: Percentages were based on the number of subjects in the Randomised Set.

Table SIII.3: Demographic characteristics of subjects in study SB16-3001 (Randomised Set)

Characteristics	OBODENCE (N = 225)	PROLIA (EU sourced)			Total (N = 457)
		Overall (N = 232)	OBODENCE (N = 100)[a]	PROLIA (N = 101)[a]	
Age (years)					
Mean (SD)	66.5 (5.87)	66.3 (6.03)	65.8 (5.73)	66.4 (6.05)	66.4 (5.95)
Median	67.0	66.0	66.0	66.0	66.0

Characteristics	OBODENCE (N = 225)	PROLIA (EU sourced)			Total (N = 457)
		Overall (N = 232)	OBODENCE (N = 100) [a]	PROLIA (N = 101) [a]	
Min, max	55, 81	52, 80	55, 77	55, 80	52, 81
Age group, n (%)					
< 65 years	89 (39.6)	95 (40.9)	39 (39.0)	44 (43.6)	184 (40.3)
≥ 65 years	136 (60.4)	137 (59.1)	61 (61.0)	57 (56.4)	273 (59.7)
Race, n (%)					
Asian	18 (8.0)	23 (9.9)	10 (10.0)	11 (10.9)	41 (9.0)
White	207 (92.0)	208 (89.7)	89 (89.0)	90 (89.1)	415 (90.8)
Other	0 (0.0)	1 (0.4)	1 (1.0)	0 (0.0)	1 (0.2)
Ethnicity, n (%)					
Hispanic or Latino	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.2)
Other	225 (100.0)	231 (99.6)	100 (100.0)	101 (100.0)	456 (99.8)

EU = European Union; max = maximum; min = minimum; SD = standard deviation; US = United States.

[a] Based on subjects who had re-randomisation at Month 12, PROLIA+OBODENCE and PROLIA+PROLIA may not add up to PROLIA Overall.

Note: Percentages were based on the number of subjects in the Randomised Set.

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

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

Since no biosimilarity studies were deemed necessary using XBRYK and XGEVA, the summary of important exclusion criteria presented in this section is based on the exclusion criteria in the comparative Phase III study SB16-3001 in postmenopausal women with osteoporosis. However, any limitations of the populations not studied in clinical trials are solely based on the data available for the reference product XGEVA [10, 11].

Uncorrected vitamin D deficiency (defined as serum 25-hydroxyvitamin D level < 20 ng/mL [50 nmol/L])

Not able to tolerate long-term calcium or vitamin D supplementation or had malabsorption of calcium or vitamin D supplements

Reason for exclusion	These exclusion criteria were selected to minimise the risk to participants enrolled in the comparative study. Patients with uncorrected vitamin D deficiency or patients unable to tolerate long-term calcium and/or vitamin D supplementation are at increased risk of developing hypocalcaemia during denosumab therapy.
Is it considered to be included as missing information?	No
Rationale	Patients treated with denosumab must be adequately supplemented with calcium and vitamin D during therapy with denosumab. As such, the excluded population is not expected to be treated in clinical practice.

Hypercalcaemia or hypocalcaemia (defined as albumin-adjusted serum calcium for hypocalcaemia < 2.1 mmol/L [8.4 mg/dL] or for hypercalcaemia > 2.62 mmol/L [10.5 mg/dL])

Reason for exclusion	These exclusion criteria were selected to minimise potential bias in collected data and to minimise potential risks to study participants in the comparative study.

Is it considered to be included as missing information?	No
Rationale	Hypocalcaemia represents a contraindication for use of denosumab. The exclusion of patients with pre-existing hypercalcaemia from the comparative study has no impact on the safety in this patient population, if treated in clinical practice.

History of osteonecrosis of jaw, osteonecrosis of external auditory canal, or atypical femoral fracture at Screening or related risk based on the physical examination including oral

History of active periodontal disease or invasive dental procedure within 6 months prior to Screening or planned to have invasive dental procedures (e.g., tooth extraction, dental implants, or oral surgery) during the study period

Reason for exclusion	These criteria were selected to minimise potential bias in collected data and to minimise potential risks to study participants.
Is it considered to be included as missing information?	No
Rationale	Special precautions are needed during treatment of patients with risk factors for development of osteonecrosis of jaw, osteonecrosis of external auditory canal, or atypical femoral fractures. Osteonecrosis of the jaw and atypical femoral fracture represent important identified risks of denosumab therapy (refer to Part II: Module SVII). Denosumab is contraindicated in patients with unhealed lesions from dental or oral surgery.

Fracture (except atypical femoral fracture and hip fracture) that had been actively healing within 12 months prior to Screening

Reason for exclusion	These criteria were selected to minimise potential bias in collected data and to minimise potential risks to study participants.
Is it considered to be included as missing information?	No
Rationale	The safety profile of denosumab is not expected to differ in patients with a history of (typical) fractures.

History of clinically significant active infection within 2 weeks prior to Randomisation, and for cellulitis, erysipelas, or infections that required hospitalisation or intravenous antibiotics, within 8 weeks prior to Randomisation

Reason for exclusion	These criteria were selected to minimise potential bias in collected data and to minimise potential risks to study participants.
Is it considered to be included as missing information?	No
Rationale	The safety profile of denosumab is not expected to differ in patients with a history of infection.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions, such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.1: 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 programme.
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiac impairment	Not included in the clinical development programme or not specifically studied.
Population with relevant different ethnic origin	Refer to Table SIII.2 and Table SIII.3.
Subpopulations carrying relevant genetic polymorphisms	Not applicable.
Other	Not applicable.

Part II: Module SV - Post-authorisation experience

XBRYK has not yet been approved for marketing in any country.

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

Potential for misuse for illegal purposes

The potential for misuse for illegal purposes is considered negligible, given the mechanism of action of denosumab.

Part II: Module SVII - Identified and potential risks

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

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

There are currently no risks considered as not important for inclusion in the list of safety concerns in respect to this RMP.

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

The safety concerns in the RMP for the biosimilar product XBRYK are aligned with the safety concerns for the reference product XGEVA [11] and the potential unique characteristics of the XBRYK medicinal product.

Important identified risk(s):

- **Osteonecrosis of the jaw**

Risk-benefit impact:

Osteonecrosis of the jaw is a common, serious, and potentially life-threatening adverse effect associated with denosumab therapy. Considering the benefits of denosumab therapy and risk minimisation measures in place, the impact of this risk on the benefit risk balance of denosumab is acceptable.

- **Atypical femoral fracture**

Risk-benefit impact:

Atypical femoral fractures represent serious adverse effects associated with antiresorptive medication, including denosumab. Considering the benefits of denosumab therapy and risk minimisation measures in place, the impact of this risk on the benefit risk balance of denosumab is acceptable.

- **Hypercalcemia several months after the last dose in patients with giant cell tumour of bone and in patients with growing skeletons**

Risk-benefit impact:

Hypercalcaemia following discontinuation of denosumab is a serious and potentially life-threatening complication requiring intensive treatment. Considering the infrequent occurrence of this event, the impact of this risk on the benefit-risk balance of denosumab is acceptable.

Important potential risk(s):

- **Cardiovascular events**

Risk-benefit impact:

Although a plausible biological link exists between denosumab and cardiovascular disease, there is no evidence from human trials to support a positive or negative effect on cardiovascular risk. Therefore, cardiovascular events represent a theoretical risk associated with denosumab.

Considering the benefits of therapy, the impact of this potential risk on the benefit risk balance of denosumab remains acceptable.

- **Malignancy**

Risk-benefit impact:

Malignancy represents a theoretical risk of denosumab treatment, based on denosumab immunomodulatory effects. However, no evidence for the association between the onset of malignancy and denosumab treatment was collected to date. Considering the benefits of therapy, the impact of this potential risk on the benefit risk balance of denosumab remains acceptable.

- **Delay in diagnosis of primary malignancy in giant cell tumour of bone**

Risk-benefit impact:

Delay in diagnosis of primary malignancy in giant cell tumour of bone represents a theoretical risk of denosumab treatment. Considering the benefits of therapy, the impact of this potential risk on the benefit-risk balance of denosumab remains acceptable.

- **Hypercalcemia several months after the last dose in patients other than those with giant cell tumour of bone or growing skeletons**

Risk-benefit impact:

Hypercalcaemia following discontinuation of denosumab is a serious and potentially life-threatening complication, requiring intensive treatment. Considering the infrequent occurrence of this event and unconfirmed link with denosumab in this patient population, the impact of this risk on the benefit-risk balance of denosumab is acceptable.

Missing information:

- **Patients with prior intravenous bisphosphonate treatment**

Risk-benefit impact:

The safety profile of denosumab is not expected to differ when used in patients with prior intravenous bisphosphonate treatment, but the use of denosumab in this population requires further characterisation.

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

Risk-benefit impact:

The safety profile of denosumab is not expected to differ when used long term in adults and skeletally mature adolescents with giant cell tumour of bone, but the use of denosumab in this population requires further characterisation.

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

Risk-benefit impact:

The safety profile of denosumab is not expected to differ when used off label in patients with giant cell tumour of bone that is resectable where resection is unlikely to result in severe morbidity, but the use of denosumab in this population requires further characterisation.

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

Not applicable.

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

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

Important identified risk 1: Osteonecrosis of the jaw

Potential mechanisms:

The mechanism for denosumab-induced osteonecrosis of the jaw has not yet been elucidated but appears to be multi-factorial.

Several potential mechanisms have been hypothesised, including over suppression of bone remodelling, local infection, inhibition of angiogenesis, soft tissue toxicity, and immune dysfunction [12].

Inhibition of osteoclastic activity, mediated by denosumab, has also been hypothesised as a potential mechanism for the development of osteonecrosis of the jaw [13].

Evidence source(s) and strength of evidence:

This risk is based on the safety profile of denosumab as reflected in the Product Information and the summary of safety concerns for the reference product XGEVA [10, 11].

Characterisation of the risk:

Frequency, severity, and nature of the risk (including reversibility and long-term outcomes)

The frequency of osteonecrosis of the jaw in association with denosumab is 'common' (i.e., ≥ 1 in 100 to < 1 in 10), based on the overall experience with denosumab from Phase II and Phase III clinical studies and the post-marketing experience [10].

No events of osteonecrosis of the jaw were reported in the comparative Phase III study SB16-3001 within the OBODENCE programme in either treatment group in the Overall Study Period (Safety Set 1).

A non-randomised, retrospective, observational study analysing data from 2,877 patients with cancer treated with denosumab or zoledronic acid in Sweden, Denmark, and Norway showed that the 5-year incidence proportions of medically confirmed osteonecrosis of the jaw were 5.7% among patients receiving denosumab, 1.4% among patients receiving zoledronic acid, and 6.6% among patients switching to denosumab after no more than 24 monthly cancer doses of bisphosphonates [14].

In the above study, the incidence proportion of osteonecrosis of the jaw increased with follow-up time more prominently in the denosumab cohorts than the zoledronic acid cohort; this was possibly related to a greater median number of monthly doses received by patients in the denosumab cohorts [14].

Osteonecrosis of the jaw is a serious complication of denosumab therapy, characterised by persistent, often painful necrosis of bone in the maxillofacial region, which reduces quality of

life and is associated with significant morbidity [12, 15]. Osteonecrosis of the jaw may lead to jawbone infections, chronic pain, and tooth loss and compromised function [16].

While moderate to severe cases are the most frequent, life-threatening cases complicated by sepsis were also reported [17, 18].

Denosumab-associated osteonecrosis of the jaw was shown to be reversible in some cases upon denosumab discontinuation [19, 20]. Other reports showed more complete healing only following a major surgery, with no effect of denosumab discontinuation on healing [21].

The literature further reports that the success rate of conservative treatment regimens range from less than 20% to above 50%, although some cases become chronic and develop complications [20]. There is no consensus on the treatment of denosumab-associated osteonecrosis of the jaw but surgery indicated as an early treatment was shown to prevent complications and the progression of the lesions [18].

No data on the long-term outcomes are available.

Risk factors and risk groups:

The following risk factors should be considered when evaluating a patient's risk of developing osteonecrosis of the jaw:

- potency of the medicinal product that inhibits bone resorption (higher risk for highly potent compounds), route of administration (higher risk for parenteral administration) and cumulative dose of bone resorption therapy
- cancer, co-morbid conditions (e.g., anaemia, coagulopathies, diabetes mellitus, infection), smoking
- concomitant therapies: corticosteroids, chemotherapy, angiogenesis inhibitors, radiotherapy to head and neck
- poor oral hygiene, periodontal disease, poorly fitting dentures, history of dental disease, invasive dental procedures (e.g., tooth extractions).

The general risk factors for the development of osteonecrosis of the jaw associated with anti-osteoporotic medication include [12, 22, 23]:

- 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
- vascular insufficiency due to thrombosis.

Preventability:

The start of treatment/new treatment course should be delayed in patients with unhealed open soft tissue lesions in the mouth. A dental examination with preventive dentistry and an individual benefit-risk assessment is recommended prior to treatment with denosumab in patients with concomitant risk factors.

All patients should be encouraged to maintain good oral hygiene, receive routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain or swelling or non-healing of sores or discharge during treatment with denosumab.

While on treatment, invasive dental procedures should be performed only after careful consideration and be avoided in close proximity to denosumab administration.

The management plan of the patients who develop osteonecrosis of the jaw should be set up in close collaboration between the treating physician and a dentist or oral surgeon with expertise in osteonecrosis of the jaw.

Temporary interruption of treatment should be considered until the condition resolves and contributing risk factors are mitigated where possible.

Refer to Part V.2, detailing the additional risk minimisation measures in place for this risk.

Impact on the risk-benefit balance of the product:

Osteonecrosis of the jaw is a common, serious, and potentially life-threatening adverse effect associated with denosumab therapy. Considering the benefits of denosumab therapy and risk minimisation measures in place, the impact of this risk on the benefit-risk balance of denosumab is acceptable.

Public health impact:

No impact on public health is expected.

Important identified risk 2: Atypical femoral fracture

Potential mechanisms:

The mechanism for development of atypical femoral fractures remains poorly understood, although a number of mechanisms have been proposed [24].

Radiologic features seen in atypical femoral fractures are consistent with stress fractures, which occur when bones are subjected to repetitive loading that overwhelms the capacity for bone repair. Antiresorptive medications, including denosumab, which suppress bone remodelling, may result in accumulation of micro-damage which is not repaired, thus leading to the development of stress fractures [24].

Evidence source(s) and strength of evidence:

This risk is based on the safety profile of denosumab as reflected in the Product Information and the summary of safety concerns for the reference product XGEVA [10, 11].

Characterisation of the risk:

Frequency, severity, and nature of the risk (including reversibility and long-term outcomes)

The frequency of atypical femoral fractures in association with denosumab is 'uncommon' (i.e., ≥ 1 in 1,000 to < 1 in 100), based on the overall experience with denosumab from Phase II and Phase III clinical studies and the post-marketing experience [10].

No events of atypical femoral fractures were reported in the comparative Phase III study SB16-3001 within the OBODENCE programme in either treatment group in the Overall Study Period (Safety Set 1).

Atypical femoral fractures associated with denosumab may occur with little or no trauma in the subtrochanteric and diaphyseal regions of the femur and have specific radiographic findings [24]. Similar fractures reported in association with bisphosphonates are often bilateral.

A high percentage of patients affected with atypical femoral fractures experience prodromal thigh/groin pain [25, 26].

Atypical femoral fractures are serious events, usually requiring medical interventions, including surgery and ongoing monitoring. Appropriate exercise guidance is important for patients affected with atypical femoral fractures, because repetitive stress to the lower limbs can cause further bone damage and slow fracture healing [24].

No data on the reversibility of the pathophysiological mechanism upon denosumab discontinuation or on the long-term outcomes are available. However, available data suggest that healing of atypical femoral fractures can be prolonged in comparison to the typical fractures [25, 26]. Because of the propensity for delayed healing, the morbidity of these fractures is particularly high [26].

Atypical femoral fractures have a potentially significant impact on patients' quality of life, leading to short- or long-term disability.

Risk factors and risk groups:

The risk of atypical femoral fractures seems to increase with the duration of therapy [24, 26].

Observational studies showed that women are at increased risk compared to men and Asian women are more prone to atypical femoral fraction compared to White women [24].

The presence of a genetic metabolic bone disorder may be an important risk factor for developing atypical femoral fractures [24].

Atypical femoral fractures have been reported in patients with certain co-morbid conditions (e.g., vitamin D deficiency, rheumatoid arthritis, hypophosphatasia) and with use of certain medicinal products (e.g., bisphosphonates, glucocorticoids, proton pump inhibitors) [24, 26, 27]. These events have also occurred without antiresorptive therapy.

Preventability:

Discontinuation of denosumab therapy in patients suspected to have an atypical femoral fracture should be considered pending evaluation of the patient based on an individual benefit-risk assessment.

Similar fractures reported in association with bisphosphonates are often bilateral. Therefore, the contralateral femur should be examined in denosumab-treated patients who have sustained a femoral shaft fracture.

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.

Impact on the risk-benefit balance of the product:

Atypical femoral fractures represent serious adverse effects associated with antiresorptive medication, including denosumab. Considering the benefits of denosumab therapy and risk minimisation measures in place, the impact of this risk on the benefit risk balance of denosumab is acceptable.

Public health impact:

No impact on public health is expected.

Important identified risk 3: Hypercalcemia several months after the last dose in patients with giant cell tumour of bone and in patients with growing skeletons

Potential mechanisms:

The mechanism for development of hypercalcaemia several months after treatment discontinuation has not yet been fully elucidated but is most likely caused by the rapid recovery of osteoclastic activity, triggering the surge of bone resorption and the release of calcium from the calcified tissue into the circulation [28]. This concept indicates that bone turnover rate and the amount of overstored calcium determine the severity of the increase in serum calcium following denosumab discontinuation.

Hypercalcaemia has been reported in skeletally immature patients treated with varying denosumab doses [28]. Rebound hypercalcaemia was reported in adult patients with giant cell tumour of bone treated with 120 mg denosumab [28, 29].

Evidence source(s) and strength of evidence:

This risk is based on the safety profile of denosumab as reflected in the Product Information and the summary of safety concerns for the reference product XGEVA [10, 11].

Characterisation of the risk:

Frequency, severity, and nature of the risk (including reversibility and long-term outcomes)

The frequency of hypercalcaemia following treatment discontinuation in patients with giant cell tumour of bone is ‘uncommon’ (i.e., ≥ 1 in 1,000 to < 1 in 100), based on the overall experience with denosumab from Phase II and Phase III clinical studies and the post-marketing experience [10].

The mean half-life of denosumab after cessation is reported to be 29 days (range: 25 to 35 days). However, the clearance is likely to be longer in individuals with accumulated doses, hence the occurrence of rebound hypercalcaemia as late as 7 months from treatment cessation [29].

General symptoms of hypercalcaemia include excessive thirst, excessive urination, drowsiness, confusion, loss of concentration, feeling or being sick, constipation, and muscle weakness. Severe hypercalcaemia can cause serious kidney problems (acute renal injury), coma, heart rhythm abnormalities, and cardiac arrest [30].

Given the current state of knowledge, the exact timing of onset of hypercalcemia cannot be anticipated [31]. The literature shows that rebound hypercalcaemia often occurs within 3 months after the last dose of denosumab in children and adolescents, but later than 3 months in skeletally mature adults [28].

Rebound hypercalcaemia is often intractable and requires intensive treatment as it usually responds poorly to hydration alone and the literature described the administration of diuretics, corticosteroids, and/or calcitonin. In severe cases, repeated use of bisphosphonates (zoledronate, pamidronate, ibandronate) or reinjection of denosumab was often required to repress the surge of calcium released into the circulation [28, 29]. Although the prolonged antiresorptive action of bisphosphonates is an effective treatment of hypercalcaemia, in the context of hypercalcaemia, the presence of acute kidney injury increases the risk of bisphosphonate-induced renal failure [29].

Risk factors and risk groups:

The specific risk factors or risk groups for rebound hypercalcaemia associated with denosumab have not yet been established.

Preventability:

No specific preventive measures have yet been established for denosumab.

Gradual decrease of the denosumab dose and prophylactic use of bisphosphonates has been attempted; however, the clinical benefits of these measures are currently unknown [28].

Impact on the risk-benefit balance of the product:

Hypercalcaemia following discontinuation of denosumab is a serious and potentially life-threatening complication, requiring intensive treatment. Considering the infrequent occurrence of this event, the impact of this risk on the benefit-risk balance of denosumab is acceptable.

Public health impact:

No impact on public health is expected.

Important potential risk 1: Cardiovascular events

Potential mechanisms:

Denosumab mimics the natural action of osteoprotegerin (OPG) [33, 34]. OPG is a soluble decoy receptor of RANKL, preventing RANKL from binding to RANK on osteoclast and osteoclasts precursors and inhibiting bone resorption [32, 35]. The increased RANKL/OPG ratio is described among the inflammatory mechanisms associated with atherosclerosis [36].

RANKL is produced by the main cells involved in the atherosclerotic process in response to inflammatory stimuli (activated T lymphocytes, endothelial and vascular smooth muscle cells), while studies in mice have demonstrated that OPG has protective role in vascular calcification [36, 37].

Genetically modified animals that lack the gene for OPG have increased vascular calcification and osteoporosis, indicating a potential protective role of OPG. Moreover, exogenous OPG has been shown to have mitigating effects on vascular calcification in animal models of atherosclerosis and calcific arteriopathy [35].

However, the exact role of RANKL and OPG in the vascular compartment is unclear, because preclinical findings are not consistent with human epidemiological observations [35].

Evidence source(s) and strength of evidence:

This risk is based on the safety profile of denosumab as reflected in the Product Information and the summary of safety concerns for the reference product XGEVA [10, 11].

Characterisation of the risk:

Frequency, severity, and nature of the risk (including reversibility and long-term outcomes)

The frequency and nature of risk of cardiovascular events potentially associated with denosumab has not yet been established.

The incidence of cardiovascular event was comparable between the OBODENCE and PROLIA. Overall treatment groups within the comparative Phase III study SB16-3001 and the overall incidence was 2.2% (5/225 subjects) for OBODENCE and 3.0% (7/231 subjects) for the PROLIA Overall treatment groups within the Overall Study Period (Safety Set 1). Reported cardiovascular events included coronary artery disease, acute myocardial infarction, atrial fibrillation, chronic cardiac failure, myocardial ischemia, carotid artery stenosis, cerebral small vessel disease, intracranial aneurysm and transient ischemic attack. One subject (0.4%) in OBODENCE and two subjects (0.8%) in PROLIA Overall treatment groups experienced serious events of cardiovascular events.

Although a plausible biological link exists between denosumab and cardiovascular disease, there is no evidence from clinical trials to support a positive or negative effect on cardiovascular risk, at least at the dose used in osteoporosis therapy [38].

A further analysis of a subset of 2,363 women (1,142 placebo, 1,221 denosumab [PROLIA]) with osteoporosis from the FREEDOM trial who were at high risk of cardiovascular disease was conducted [35]. In this study, aortic calcification and progression was assessed using a semi-quantitative method from lateral spine radiographs. There was no significant difference in aortic calcification progression over the 3 years of the trial between the placebo (22%) and denosumab (22%) groups and no difference in cardiovascular risk across the two groups (in the high cardiovascular risk population) [35].

Risk factors and risk groups:

The specific risk factors or risk groups for cardiovascular events potentially associated with denosumab have not yet been established.

The general risk factor for cardiovascular events and atherosclerosis include older age, sex, ethnicity, family history, elevated lipid levels, cigarette smoking, hypertension, diabetes mellitus, and medications, including antipsychotics or cyclooxygenase-2 inhibitors.

Preventability:

No specific preventability measures have been established for denosumab.

Impact on the risk-benefit balance of the product:

Although a plausible biological link exists between denosumab and cardiovascular disease, there is no evidence from human trials to support a positive or negative effect on cardiovascular risk. Therefore, cardiovascular events represent a theoretical risk associated with denosumab. Considering the benefits of therapy, the impact of this potential risk on the benefit-risk balance of denosumab remains acceptable.

Public health impact:

No impact on public health is expected.

Important potential risk 2: Malignancy

Potential mechanisms:

Since denosumab possesses immunomodulatory effect, concerns exists about its potential to cause malignancy [33]. RANKL and RANK are expressed by immune cells (e.g., activated T cells, B cells, dendritic cells) and it has therefore been theorised that inhibition of RANKL might increase the risk of infections and/or malignancy [32].

It should be noted that one of the mechanisms of enhancing tumour cell survival by OPG is inhibition of tumour necrosis factor (TNF)-related apoptosis inducing ligand (TRAIL)-induced apoptosis; yet, an in-vitro observation showed that denosumab differs from OPG since it binds only to human and nonhuman primate RANKL and not to any other member of the TNF family including human TRAIL [33].

Evidence source(s) and strength of evidence:

This risk is based on the safety profile of denosumab as reflected in the Product Information and the summary of safety concerns for the reference product XGEVA [10, 11].

Characterisation of the risk:

Frequency, severity, and nature of the risk (including reversibility and long-term outcomes)

The frequency of new primary malignancy is ‘common’ (i.e., ≥ 1 in 100 to < 1 in 10), based on the overall experience with denosumab from Phase II and Phase III clinical studies and the post-marketing experience [10].

The incidence of malignancies was comparable between the OBODENCE and PROLIA Overall treatment groups within the comparative Phase III study SB16-3001 within the OBODENCE programme and the overall incidence was 0.4% (1/225 subjects) for OBODENCE and 0.9% (2/231 subjects) for the PROLIA Overall treatment groups within the Overall Study Period (Safety Set 1).

The nature of the risk of malignancy potentially associated with denosumab has not yet been established.

Risk factors and risk groups:

The specific risk factors or risk groups for the onset of malignancy potentially associated with denosumab have not yet been established.

The general factors for risk of malignancy include advancing age, diet, cigarette smoking, excessive ethanol consumption, and numerous environmental toxins.

Preventability:

No specific preventability measures have been established for denosumab.

Impact on the risk-benefit balance of the product:

Malignancy represents a theoretical risk of denosumab treatment, based on denosumab's immunomodulatory effects. However, no evidence for the association between the onset of malignancy and denosumab treatment was collected to date. Considering the benefits of therapy, the impact of this potential risk on the benefit-risk balance of denosumab remains acceptable.

Public health impact:

No impact on public health is expected.

Important potential risk 3: Delay in diagnosis of primary malignancy in giant cell tumour of bone

Potential mechanisms:

Based on the mechanism of action, denosumab is only expected to treat benign giant cell tumour of bone. However, there is a theoretical concern that denosumab could be used to treat an undiagnosed primary malignancy in giant cell tumour of bone, which could delay the diagnosis of the primary malignancy.

Diagnosis of malignancy in giant cell tumour of bone can be challenging because radiologic features of primary malignancy are often identical to those of benign giant cell tumour of bone [39-41]. Furthermore, there is a high level of heterogeneity among primary malignant tumours [39, 41]. The lack of clear diagnostic criteria for malignant giant cell tumour of bone further complicates diagnosis [41].

The main pathological feature that represents a potential misdiagnosis is the presence of a giant cell component that can be present in other malignant mesenchymal tumours. Other features may include poor mineralization or rapid relapse in pain or no pain relief during treatment with denosumab [41].

Evidence source(s) and strength of evidence:

This risk is based on the safety profile of denosumab as reflected in the Product Information and the summary of safety concerns for the reference product XGEVA [10, 11].

Characterisation of the risk:

Frequency, severity, and nature of the risk (including reversibility and long-term outcomes)

In a Phase II study on 526 patients with pathologically confirmed giant cell tumour of bone and measurable active disease receiving denosumab 120 mg, 20 patients (3.8%) were misdiagnosed with giant cell tumour of bone that was later discovered to be a malignancy. Of these, 5 patients (1.0%) had a primary malignant giant cell tumour of bone [41].

The severity and nature of this risk have not been established for denosumab.

Risk factors and risk groups:

No specific risk factors have been recognised.

All patients with giant cell tumour of bone receiving denosumab are at risk of a delayed diagnosis of primary malignant giant cell tumour of bone.

Preventability:

No specific preventability measures have been established for denosumab.

Impact on the risk-benefit balance of the product:

Delay in diagnosis of primary malignancy in giant cell tumour of bone represents a theoretical risk of denosumab treatment. Considering the benefits of therapy, the impact of this potential risk on the benefit-risk balance of denosumab remains acceptable.

Public health impact:

No impact on public health is expected.

Important potential risk 4: Hypercalcemia several months after the last dose in patients other than those with giant cell tumour of bone or growing skeletons

Potential mechanisms:

As previously discussed, the mechanism for development of hypercalcaemia several months after treatment discontinuation is most likely caused by the rapid recovery of osteoclastic activity, triggering the surge of bone resorption and the release of calcium from the calcified tissue into the circulation [28]. Based on this concept, the severity of the increase in serum calcium following denosumab discontinuation is determined by the bone turnover rate and the amount of overstored calcium.

The duration of denosumab treatment required to trigger hypercalcemia is longer in skeletally mature adults compared to paediatric patients. Furthermore, the time from the last denosumab injection to the onset of hypercalcemia is significantly longer for skeletally mature adults (5.75 months) compared with paediatric patients (4 months) [28].

Evidence source(s) and strength of evidence:

This risk is based on the safety profile of denosumab as reflected in the Product Information and the summary of safety concerns for the reference product XGEVA [10, 11].

Characterisation of the risk:

Frequency, severity, and nature of the risk (including reversibility and long-term outcomes)

The frequency, severity, and nature of hypercalcaemia following treatment discontinuation in patients other than those with giant cell tumour of bone or growing skeletons have not yet been established.

As previously discussed, general symptoms of hypercalcaemia include excessive thirst, excessive urination, drowsiness, confusion, loss of concentration, feeling or being sick, constipation, and muscle weakness. Severe hypercalcaemia can cause serious kidney problems (acute renal injury), coma, heart rhythm abnormalities, and cardiac arrest [30].

Given the current state of knowledge, the exact timing of onset of hypercalcemia cannot be anticipated [31]. The literature shows that rebound hypercalcaemia often occurs within 3 months after the last dose of denosumab in children and adolescents, but later than 3 months in skeletally mature adults [28].

Rebound hypercalcaemia is often intractable and requires intensive treatment as it usually responds poorly to hydration alone and the literature described the administration of diuretics, corticosteroids, and/or calcitonin. In severe cases, repeated use of bisphosphonates (zoledronate, pamidronate, ibandronate) or reinjection of denosumab was often required to repress the surge of calcium released into the circulation [28, 29]. Although the prolonged antiresorptive action of bisphosphonates is an effective treatment of hypercalcaemia, in the context of hypercalcaemia, the presence of acute kidney injury increases the risk of bisphosphonate-induced renal failure [29].

Risk factors and risk groups:

The specific risk factors or risk groups for rebound hypercalcaemia associated with denosumab have not yet been established.

Preventability:

No specific preventive measures have yet been established for denosumab.

As previously discussed, gradual decrease of the denosumab dose and prophylactic use of bisphosphonates has been attempted; however, the clinical benefits of these measures are currently unknown [28].

Impact on the risk-benefit balance of the product:

Hypercalcaemia following discontinuation of denosumab is a serious and potentially life-threatening complication, requiring intensive treatment. Considering the infrequent occurrence of this event, the impact of this risk on the benefit-risk balance of denosumab is acceptable.

Public health impact:

No impact on public health is expected.

SVII.3.2 Presentation of the missing information

Missing information 1: Patients with prior intravenous bisphosphonate treatment

Evidence source:

This missing information is based on the safety profile of denosumab as reflected in the Product Information and the summary of safety concerns for the reference product XGEVA [10, 11].

Anticipated risk/consequence of the missing information:

The safety profile of denosumab is not expected to differ when used in patients with prior intravenous bisphosphonate treatment, but the use of denosumab in this population requires further characterisation.

Missing information 2: Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumour of bone

Evidence source:

This missing information is based on the safety profile of denosumab as reflected in the Product Information and the summary of safety concerns for the reference product XGEVA [10, 11].

Anticipated risk/consequence of the missing information:

The safety profile of denosumab is not expected to differ when used long term in adults and skeletally mature adolescents with giant cell tumour of bone, but the use of denosumab in this population requires further characterisation.

Missing information 3: Off-label use in patients with giant cell tumour of bone that is resectable where resection is unlikely to result in severe morbidity

Evidence source:

This missing information is based on the safety profile of denosumab as reflected in the Product Information and the summary of safety concerns for the reference product XGEVA [10, 11].

Anticipated risk/consequence of the missing information:

The safety profile of denosumab is not expected to differ when used off label in patients with giant cell tumour of bone that is resectable where resection is unlikely to result in severe morbidity, but the use of denosumab in this population requires further characterisation.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

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

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

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

- **Specific adverse reaction follow-up questionnaire for osteonecrosis of the jaw**

This questionnaire is designed to obtain structured information on the denosumab-associated osteonecrosis of the jaw to characterise the nature of this risk associated with denosumab and to monitor the reporting rate in clinical practice.

This form aims to collect detailed information about the patient, concerned medicinal product, patient's history, clinical presentation of the event, and information on the treatment.

- **Specific adverse reaction follow-up questionnaire for atypical femoral fracture**

This questionnaire is designed to obtain structured information on the denosumab-associated atypical femoral fractures to characterise the nature of this risk associated with denosumab and to monitor the reporting rate in clinical practice.

This form aims to collect detailed information about the patient, concerned medicinal product, patient's history, clinical presentation of the event, and information on the treatment.

The respective questionnaires are provided in Annex 4.

III.2 Additional pharmacovigilance activities

There are no ongoing or planned additional pharmacovigilance activities.

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)

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

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

Safety concern	Routine risk minimisation activities
Osteonecrosis of the jaw	Routine risk communication SmPC sections 4.3, 4.4, 4.8, and 5.1 PL sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation for dental examination with preventive dentistry and individual benefit-risk assessment of patients prior to treatment with denosumab is included in SmPC section 4.4. Recommendation that invasive dental procedures while on treatment with denosumab are performed only after careful consideration and avoided in close proximity to denosumab administration is included in SmPC section 4.4. Other routine risk minimisation measures beyond the Product Information: Subject to restricted medical prescription
Atypical femoral fracture	Routine risk communication SmPC sections 4.4 and 4.8 PL sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation for examining the contralateral femur in denosumab-treated patients who have sustained a femoral shaft fracture is included in SmPC section 4.4. Recommendation for evaluating patients presenting with new or unusual thigh, hip or groin pain for an incomplete femoral fracture is included in SmPC section 4.4. Other routine risk minimisation measures beyond the Product Information: Subject to restricted medical prescription

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

Safety concern	Routine risk minimisation activities
Hypercalcemia several months after the last dose in patients with giant cell tumour of bone and in patients with growing skeletons	Routine risk communication SmPC sections 4.4 and 4.8 PL sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation for monitoring patients for signs and symptoms of hypercalcaemia, periodic assessment of serum calcium, and re-evaluation of the patients' calcium and vitamin D supplementation requirements is included in SmPC section 4.4. Other routine risk minimisation measures beyond the Product Information: Subject to restricted medical prescription
Cardiovascular events	Routine risk communication None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Subject to restricted medical prescription
Malignancy	Routine risk communication SmPC sections 4.4, 4.8. and 5.1 PL section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation for monitoring patients for radiological signs of malignancy, new radiolucency or osteolysis is included in SmPC section 4.4. Other routine risk minimisation measures beyond the Product Information: Subject to restricted medical prescription

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

Safety concern	Routine risk minimisation activities
Delay in diagnosis of primary malignancy in giant cell tumour of bone	Routine risk communication None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Subject to restricted medical prescription
Hypercalcemia several months after the last dose in patients other than those with giant cell tumour 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 measures beyond the Product Information: Subject to restricted medical prescription
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 measures beyond the Product Information: Subject to restricted medical prescription
Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumour of bone	Routine risk communication None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information:

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

Safety concern	Routine risk minimisation activities
	Subject to restricted medical prescription
Off-label use in patients with giant cell tumour of bone that is resectable where resection is unlikely to result in severe morbidity	Routine risk communication None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Subject to restricted medical prescription

PL = package leaflet; SmPC = summary of product characteristics.

V.2 Additional Risk Minimisation Measures

Patient reminder card

Objectives:

The objective of the patient reminder card is to remind patients about important safety information that they need to be aware of before and during the treatment with denosumab XBRYK 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 (XBRYK) 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 sores, or discharge.

List of addressed safety concern(s):

- Osteonecrosis of the jaw

Rationale for the additional risk minimisation activity:

Osteonecrosis of the jaw is a rare but serious adverse effect associated with denosumab therapy. The patient reminder card was designed to provide patients with important safety information that they need to be aware before and during treatment with denosumab.

Target audience and planned distribution path:

The target audience for this card is represented by patients treated with XBRYK.

These cards are distributed to the prescribers with instructions to provide these to patients or as agreed on a national level. Some national plans include making the patient reminder card available on a website.

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

Not applicable

V.3 Summary of Risk Minimisation Measures

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

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Osteonecrosis of the jaw	Routine risk minimisation SmPC sections 4.3, 4.4, 4.8, and 5.1 PL sections 2 and 4 Recommendation for examining the contralateral femur in denosumab-treated patients who have sustained a femoral shaft fracture is included in SmPC section 4.4. Recommendation for evaluating patients presenting with new or unusual thigh, hip or groin pain for an incomplete femoral fracture is included in SmPC section 4.4. Subject to restricted medical prescription Additional risk minimisation Patient reminder card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities None
Atypical femoral fracture	Routine risk minimisation SmPC sections 4.4 and 4.8 PL sections 2 and 4 Recommendation for examining the contralateral femur in denosumab-treated patients who have sustained a femoral shaft fracture is included in SmPC section 4.4.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities None

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

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Recommendation for evaluating patients presenting with new or unusual thigh, hip or groin pain for an incomplete femoral fracture is included in SmPC section 4.4. Subject to restricted medical prescription Additional risk minimisation None	
Hypercalcemia several months after the last dose in patients with giant cell tumour of bone and in patients with growing skeletons	Routine risk minimisation SmPC sections 4.4 and 4.8 PL sections 2 and 4 Recommendation for monitoring patients for signs and symptoms of hypercalcaemia, periodic assessment of serum calcium, and re-evaluation of the patients' calcium and vitamin D supplementation requirements is included in SmPC section 4.4. Subject to restricted medical prescription Additional risk minimisation None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection None Additional pharmacovigilance activities None
Cardiovascular events	Routine risk minimisation Subject to restricted medical prescription Additional risk minimisation None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection None Additional pharmacovigilance activities None
Malignancy	Routine risk minimisation SmPC sections 4.4, 4.8. and 5.1	Routine pharmacovigilance activities beyond adverse

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

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	PL section 4 Recommendation for monitoring patients for radiological signs of malignancy, new radiolucency or osteolysis is included in SmPC section 4.4. Subject to restricted medical prescription Additional risk minimisation None	reactions reporting and signal detection None Additional pharmacovigilance activities None
Delay in diagnosis of primary malignancy in giant cell tumour of bone	Routine risk minimisation Subject to restricted medical prescription Additional risk minimisation None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection None Additional pharmacovigilance activities None
Hypercalcemia several months after the last dose in patients other than those with giant cell tumour of bone or growing skeletons	Routine risk minimisation Subject to restricted medical prescription Additional risk minimisation None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection None Additional pharmacovigilance activities None
Patients with prior intravenous bisphosphonate treatment	Routine risk minimisation SmPC sections 4.5 and 5.1 PL section 2 Subject to restricted medical prescription Additional risk minimisation None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection None Additional pharmacovigilance activities None

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

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumour of bone	Routine risk minimisation Subject to restricted medical prescription Additional risk minimisation None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection None Additional pharmacovigilance activities None
Off-label use in patients with giant cell tumour of bone that is resectable where resection is unlikely to result in severe morbidity	Routine risk minimisation Subject to restricted medical prescription Additional risk minimisation None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection None Additional pharmacovigilance activities None

PL = package leaflet; SmPC = summary of product characteristics.

Part VI: Summary of the risk management plan

Summary of risk management plan for XBRYK (denosumab)

This is a summary of the risk management plan (RMP) for XBRYK. The RMP details important risks of XBRYK, how these risks can be minimised, and how more information will be obtained about XBRYK's risks and uncertainties (missing information).

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

This summary of the RMP for XBRYK 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 XBRYK's RMP.

I. The medicine and what it is used for

XBRYK is authorised for prevention of skeletal-related events (pathological fracture, radiation to bone, spinal cord compression, or surgery to bone) in adults with advanced malignancies involving bone and for the 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 (see SmPC for the full indications). It contains denosumab as the active substance, and it is given by the subcutaneous route of administration.

Further information about the evaluation of XBRYK's benefits can be found in XBRYK's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

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

Important risks of XBRYK, together with measures to minimise such risks and the proposed studies for learning more about XBRYK's risks, are outlined below.

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

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

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

In the case of XBRYK, these measures are supplemented with *additional risk minimization 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 XBRYK is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

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

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

II.B Summary of important risks

Important identified risk: Osteonecrosis of the jaw	
Evidence for linking the risk to the medicine	This risk is based on the safety profile of denosumab as reflected in the Product Information and the summary of safety concerns for the reference product XGEVA.
Risk factors and risk groups	The following risk factors should be considered when evaluating a patient's risk of developing osteonecrosis of the jaw: • potency of the medicinal product that inhibits bone resorption (higher risk for highly potent compounds), route of administration (higher risk for parenteral administration) and cumulative dose of bone resorption therapy • cancer, co-morbid conditions (e.g., anaemia, coagulopathies, diabetes mellitus, infection), smoking • concomitant therapies: corticosteroids, chemotherapy, angiogenesis inhibitors, radiotherapy to head and neck • poor oral hygiene, periodontal disease, poorly fitting dentures, history of dental disease, invasive dental procedures (e.g., tooth extractions). The general risk factors for the development of osteonecrosis of the jaw associated with anti-osteoporotic medication include (Mehrotra and Ruggiero, 2006; Tofé et al, 2020; Everts-Graber et al, 2022): • 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

Important identified risk: Osteonecrosis of the jaw	
	• hypercoagulable state secondary to underlying malignancy • vascular insufficiency due to thrombosis.
Risk minimisation measures	Routine risk minimisation SmPC sections 4.3, 4.4, 4.8, and 5.1 PL sections 2 and 4 Recommendation for examining the contralateral femur in denosumab-treated patients who have sustained a femoral shaft fracture is included in SmPC section 4.4. Recommendation for evaluating patients presenting with new or unusual thigh, hip or groin pain for an incomplete femoral fracture is included in SmPC section 4.4. Subject to restricted medical prescription Additional risk minimisation Patient reminder card

Everts-Graber J, Lehmann D, Burkard J-P, Schaller B, Gahl B, Häuselmann H, et al. Risk of Osteonecrosis of the Jaw Under Denosumab Compared to Bisphosphonates in Patients With Osteoporosis. J Bone Miner Res. 2022;37(2):340-8.
Mehrotra B, Ruggiero S. Bisphosphonate complications including osteonecrosis of the jaw. Hematology Am Soc Hematol Educ Program. 2006:356-60, 515.
Tofé VI, Bagán L, Bagán JV. Osteonecrosis of the jaws associated with denosumab: Study of clinical and radiographic characteristics in a series of clinical cases. J Clin Exp Dent. 2020;12(7):e676-e81.

Important identified risk: Atypical femoral fracture	
Evidence for linking the risk to the medicine	This risk is based on the safety profile of denosumab as reflected in the Product Information and the summary of safety concerns for the reference product XGEVA.
Risk factors and risk groups	The risk of atypical femoral fractures seems to increase with the duration of therapy (Shane et al. 2010; Tile and Cheung 2020). Observational studies showed that women are at increased risk compared to men and Asian women are more prone to atypical femoral fraction compared to White women (Tile and Cheung 2020). The presence of a genetic metabolic bone disorder may be an important risk factor for developing atypical femoral fractures (Tile and Cheung 2020). Atypical femoral fractures have been reported in patients with certain co-morbid conditions (e.g., vitamin D

Important identified risk: Atypical femoral fracture	
	deficiency, rheumatoid arthritis, hypophosphatasia) and with use of certain medicinal products (e.g., bisphosphonates, glucocorticoids, proton pump inhibitors) (Shane et al. 2010; Meier et al. 2012; Tile and Cheung 2020). These events have also occurred without antiresorptive therapy.
Risk minimisation measures	Routine risk minimisation SmPC sections 4.4 and 4.8 PL sections 2 and 4 Recommendation for examining the contralateral femur in denosumab-treated patients who have sustained a femoral shaft fracture is included in SmPC section 4.4. Recommendation for evaluating patients presenting with new or unusual thigh, hip or groin pain for an incomplete femoral fracture is included in SmPC section 4.4. Subject to restricted medical prescription Additional risk minimisation None

Meier RP, Perneger TV, Stern R, Rizzoli R, Peter RE. Increasing occurrence of atypical femoral fractures associated with bisphosphonate use. Arch Intern Med. 2012; 172(12): 930-6.
Shane E, Burr D, Ebeling PR, Abrahamsen B, Adler RA, Brown TD, et al. Atypical subtrochanteric and diaphyseal femoral fractures: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res. 2010; 25(11): 2267-94.
Tile L, Cheung AM. Atypical femur fractures: current understanding and approach to management. Ther Adv Musculoskelet Dis. 2020; 12: 1759720x20916983.

Important identified risk: Hypercalcemia several months after the last dose in patients with giant cell tumour of bone and in patients with growing skeletons	
Evidence for linking the risk to the medicine	This risk is based on the safety profile of denosumab as reflected in the Product Information and the summary of safety concerns for the reference product XGEVA.
Risk factors and risk groups	The specific risk factors or risk groups for rebound hypercalcaemia associated with denosumab have not yet been established.
Risk minimisation measures	Routine risk minimisation SmPC sections 4.4 and 4.8 PL sections 2 and 4 Recommendation for monitoring patients for signs and symptoms of hypercalcaemia, periodic assessment of serum calcium, and re-evaluation of the patients' calcium and

Important identified risk: Hypercalcemia several months after the last dose in patients with giant cell tumour of bone and in patients with growing skeletons	
	vitamin D supplementation requirements is included in SmPC section 4.4. Subject to restricted medical prescription Additional risk minimisation None

Important potential risk: Cardiovascular events	
Evidence for linking the risk to the medicine	This risk is based on the safety profile of denosumab as reflected in the Product Information and the summary of safety concerns for the reference product XGEVA.
Risk factors and risk groups	The specific risk factors or risk groups for cardiovascular events potentially associated with denosumab have not yet been established. The general risk factor for cardiovascular events and atherosclerosis include older age, sex, ethnicity, family history, elevated lipid levels, cigarette smoking, hypertension, diabetes mellitus, and medications, including antipsychotics or cyclooxygenase-2 inhibitors.
Risk minimisation measures	Routine risk minimisation Subject to restricted medical prescription Additional risk minimisation None

Important potential risk: Malignancy	
Evidence for linking the risk to the medicine	This risk is based on the safety profile of denosumab as reflected in the Product Information and the summary of safety concerns for the reference product XGEVA.
Risk factors and risk groups	The specific risk factors or risk groups for the onset of malignancy potentially associated with denosumab have not yet been established. The general factors for risk of malignancy include advancing age, diet, cigarette smoking, excessive ethanol consumption, and numerous environmental toxins.
Risk minimisation measures	Routine risk minimisation SmPC sections 4.4, 4.8. and 5.1

	PL section 4 Recommendation for monitoring patients for radiological signs of malignancy, new radiolucency or osteolysis is included in SmPC section 4.4. Subject to restricted medical prescription Additional risk minimisation None

Important potential risk: Delay in diagnosis of primary malignancy in giant cell tumour of bone	
Evidence for linking the risk to the medicine	This risk is based on the safety profile of denosumab as reflected in the Product Information and the summary of safety concerns for the reference product XGEVA.
Risk factors and risk groups	No specific risk factors have been recognised. All patients with giant cell tumour of bone receiving denosumab are at risk of a delayed diagnosis of primary malignant giant cell tumour of bone.
Risk minimisation measures	Routine risk minimisation Subject to restricted medical prescription Additional risk minimisation None

Important potential risk: Hypercalcemia several months after the last dose in patients other than those with giant cell tumour of bone or growing skeletons	
Evidence for linking the risk to the medicine	This risk is based on the safety profile of denosumab as reflected in the Product Information and the summary of safety concerns for the reference product XGEVA.
Risk factors and risk groups	The specific risk factors or risk groups for rebound hypercalcaemia associated with denosumab have not yet been established.
Risk minimisation measures	Routine risk minimisation Subject to restricted medical prescription Additional risk minimisation None

Missing information: Patients with prior intravenous bisphosphonate treatment	
Risk minimisation measures	Routine risk minimisation SmPC sections 4.5 and 5.1 PL section 2 Subject to restricted medical prescription Additional risk minimisation 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 tumour of bone	
Risk minimisation measures	Routine risk minimisation Subject to restricted medical prescription Additional risk minimisation None

Missing information: Off-label use in patients with giant cell tumour of bone that is resectable where resection is unlikely to result in severe morbidity	
Risk minimisation measures	Routine risk minimisation Subject to restricted medical prescription Additional risk minimisation 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 XBRYK.

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

There are no studies required for XBRYK.

Part VII: Annexes

Annex 4 – Specific adverse drug reaction follow-up forms

This annex includes the specific adverse event follow-up forms for the safety concerns:

- Osteonecrosis of jaw
- Atypical femoral fracture

Questionnaire: Osteonecrosis of the Jaw

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Patient / Case Administrative Information (Please indicate dates as Mmm DD, YYYY)					
Patient Identifier		**Patient Initial**		**Gender**	☐ Male ☐ Female
Date of Event Onset				**Date of this Report**	
Weight		_____lb _____kg		**Age at Time of Event**	
Event Reported team					
Study Number *(if applicable)*				**Safety DB Case No.**	

Denosumab Administration / Information (Please indicate dates as Mmm DD, YYYY)

Denosumab Indication

☐ Postmenopausal osteoporosis

☐ Bone loss from hormone ablation therapy

Please specify diagnosis _____

_____

☐ Advanced cancer with bone metastasis

Please specify diagnosis _____

_____

☐ Other (please specify) _____

_____

☐ Don't know

Denosumab Dose

☐ 60mg SC every 6 months

☐ 120mg 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 were skipped

Questionnaire: Osteonecrosis of the Jaw

	☐ No ☐ Yes ☐ Unknown If yes, please specify_____ ☐ Doses of denosumab given after event began ☐ No ☐ Yes ☐ Unknown If yes, date of first dose following start of event

Evidence of Exposed Bone (Please indicate dates as Mmm DD, YYYY)

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

Describe:_____

Please describe location(s):

- ☐ Right maxilla (**upper** part), teeth and lateral jaw
- ☐ Left maxilla (**upper** part), teeth and lateral jaw
- ☐ Right maxilla (**upper** part), medial jaw
- ☐ Left maxilla (**upper** part), medial jaw
- ☐ Right mandible (**lower** part) teeth and lateral jaw
- ☐ Left mandible (**lower** part) teeth and lateral jaw
- ☐ Right mandible (**lower** part), medial jaw

Questionnaire: Osteonecrosis of the Jaw

☐ Left mandible (**lower** part), 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 Mmm DD, YYYY)

Date of first clinical signs/symptoms in the mouth (e.g. infection, pain, inflammation): _____

_____

Please describe the clinical signs/symptoms/location:

_____

_____

_____

_____

Consultations (Please indicate all dates as Mmm DD, YYYY)

Dental/ oral surgery / stomatology consultations: ☐ No ☐ Yes ☐ Unknown

If yes, please give date of examination _____

Please provide any consult reports, radiographs, pictures if available _____

_____

Questionnaire: Osteonecrosis of the Jaw

Treatment Information (Please indicate what treatments were administered and indicate dates as Mmm DD, 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 _____

Start date _____ Stop date _____
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 Mmm DD, YYYY)

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

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

Questionnaire: Osteonecrosis of the Jaw

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 Mmm DD, YYYY)

PO bisphosphate ☐ No ☐ Yes ☐ Unknown

If yes, agent(s) dose_____

Start date _____Stop date_____

IV bisphosphate ☐ 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 12 months ☐ 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 Mmm DD, YYYY)

Current smoker ☐ No ☐ Yes ☐ Unknown

If yes, estimated number of pack-years_____

If past smoker, stop date_____

Alcohol consumption ☐ No ☐ Yes ☐ Unknown

Questionnaire: Osteonecrosis of the Jaw

If yes, estimated of drinks per week_____

Diabetes ☐ No ☐ Yes ☐Unknown If yes, ☐Type I ☐Type II

Reporter	
Name:	
Address:	
City:	State/Province:
Email:	Postal Code:
Phone: (include country code)	

Signature _____

Date _____

Questionnaire: Postmarketing Reports of Potential Atypical Fracture (low energy, subtrochanteric/femoral shaft fractures)

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Patient / Case Administrative Information (Please indicate dates as Mmm DD, YYYY)					
Patient Identifier		**Patient Initial**		**Gender**	☐ Male ☐ Female
Date of Event Onset				**Date of this Report**	
Weight		_____lb _____kg		**Age at Time of Event**	
Event Reported Term					
Study No. *(if applicable)*				**Safety DB Case No.**	

Denosumab Administration / Information (Please indicate dates as Mmm DD, YYYY)

Denosumab Indication

☐ Postmenopausal osteoporosis

☐ Bone loss from hormone ablation therapy

Please specify diagnosis _____

_____

☐ Advanced cancer with bone metastasis

Please specify diagnosis _____

_____

☐ Other (please specify) _____

_____

☐ Don't know_____

Denosumab Dose

☐ 60mg SC every 6 months

☐ 120mg 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 were skipped
☐ No ☐ Yes ☐ Unknown

If yes, please specify_____

Doses of denosumab given after event began
☐ No ☐ Yes ☐ Unknown

Questionnaire: Postmarketing Reports of Potential Atypical Fracture (low energy, subtrochanteric/femoral shaft fractures)

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 imaging used to confirm fracture:

☐ X-ray ☐ CT scan ☐ MRI

Date of imaging at time of femur fracture (Mmm DD, YYYY): _____

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

Was this a pathological fracture associated with bone tumor or miscellaneous bone diseases (e.g. Paget's disease, fibrous dysplasia)?

☐ Yes ☐ No ☐ Unknown

Type of fracture:

☐ Transverse

☐ Oblique

☐ Spiral

☐ Not reported

Fracture radiology report includes:

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 the 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

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 (Mmm DD, 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

Questionnaire: Postmarketing Reports of Potential Atypical Fracture (low energy, subtrochanteric/femoral shaft fractures)

Simple transverse or oblique (30°) fracture with breaking of the cortex:

☐ Yes ☐ No ☐ Not reported

Diffuse cortical thickening of the proximal femoral shaft:

☐ Yes ☐ No ☐ Not reported

Treatment (Please provide dates and indicate attachments if available)

Methods to reduce and set fracture:

☐ 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

Cancer:

Evidence of any metastasis:
☐ Yes ☐ No ☐ Unknown

If yes, did metastasis involve bone?

☐ Yes ☐ No ☐ Unknown

Metastasis in femur where fracture occurred?

☐ Yes ☐ No ☐ Unknown

Prior osteoporosis therapy:

☐ Estrogen

☐ Selective estrogen receptor modulator (SERM)

☐ Bisphosphonate (please indicate)

☐ Intravenous ☐ Oral

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

☐ Parathyroid hormone

Past medical and surgical history: _____

_____

Questionnaire: Postmarketing Reports of Potential Atypical Fracture (low energy, subtrochanteric/femoral shaft fractures)

Medication history (include dose, frequency, and dates of treatment): _____

Copies of records/consults/radiology report attached? ☐ Yes ☐ No

Reporter	
Name:	
Address:	
City:	State/Province:
Email:	Postal Code:
Phone: (include country code)	

Signature _____

Date _____

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

Draft Key Messages of the Additional Risk Minimisation Measures

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

The educational programme is aimed at reminding to patients about the risk of osteonecrosis of the jaw associated with denosumab therapy.

The MAH shall ensure that in each Member State where XBRYK is marketed, all healthcare professionals who are expected to prescribe XBRYK have access to/are provided with the following educational package:

- Patient reminder card

Patient reminder cards for osteonecrosis of the jaw will be distributed to prescribers of XBRYK with background information on the purpose of the patient reminder card and instructions to provide it to patients.

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 the treatment with denosumab (XBRYK) 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 (XBRYK) 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 sores, or discharge.