EU Risk Management Plan
Conexxence (denosumab 60 mg)

Marketing Authorization Holder (MAH)	Fresenius Kabi Deutschland GmbH Else-Kroener-Strasse 1 61352 Bad Homburg Germany
EU RMP Version Number	2.0
Data lock point for this RMP	03-Dec-2023
Date of Final Sign-Off	See QPPV signature section below
Rationale for submitting an updated RMP	RMP referencing the company invented name
Summary of significant changes in this RMP	• Company code (FKS518) changed to brand name Conexxence
Other RMP versions under evaluation	Not applicable
Details of the currently approved RMP	Not applicable
EU QPPV name	Marcus Metternich
EU QPPV signature	

Table of contents

List of tables

Abbreviations

Abbreviation	Definition/Description
AAC	Area above the curve
AESI	Adverse Event of Special Interest
AE	Adverse Events
AFF	Atypical femoral fracture
AIDS	Acquired immune deficiency syndrome
AUC	Area under the curve
BMD	Bone mineral density
CI	Confidence interval
CrCI	Creatinine clearance
CV	Cardiovascular
EMA	European Medicine Agency
EPAR	European Public Assessment Report
EU	European Union
GC	Glucocorticoid
GCTB	Giant cell tumour of bone
HALT	Hormone ablation therapy
HR	Hazard ratio
IgG2	Immunoglobulin G2
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
NPM	New primary malignancy
OI	Osteogenesis imperfecta
ONJ	Osteonecrosis of the jaw
OPG	Osteoprotegerin
PSUR	Periodic Safety Update Report
PIL	Patient Information Leaflet
PMGCTB	Primary malignancy in giant cell tumour of bone
PMO	Postmenopausal osteoporosis
PT	Preferred Term
PY	Person-years

Abbreviation	Definition/Description
Q4W	Every 4 weeks
Q3M	Every 3 months
Q6M	Every 6 months
RA	Rheumatoid arthritis
RANK	Receptor activator of nuclear factor kappa-B
RANKL	Receptor activator of nuclear factor kappa-B ligand
RMP	Risk Management Plan
SAEs	Serious Adverse Events
SC	Subcutaneous
SmPC	Summary of Product Characteristics
SMQs	Standardized Medical Dictionary for Regulatory Activities Queries
SOC	System Organ Class
SRE	Skeletal-related event
ULN	Upper Limit of Normal
US	United States

Part I: Product(s) Overview

Product(s) Overview

Active substance(s) (INN or common name)	Denosumab
Pharmacotherapeutic group(s) (ATC Code)	M05BX04
Marketing Authorization Applicant	Fresenius Kabi Deutschland GmbH
Medicinal products to which this RMP refers	1
Company code	FKS518
Invented name(s)	Conexxence
Marketing authorization procedure	Centralised Procedure, art. 10(4) similar biological application
Brief description of the product	Chemical class Denosumab is a fully human immunoglobulin G2 (IgG) monoclonal antibody.
	Summary of mode of action Denosumab has high affinity and specificity for the soluble and cell membrane-bound forms of human receptor activator of nuclear factor kappa-B (RANK) ligand (RANKL).
	Important information about its composition Denosumab is derived from the Xeno-mouse™ technology and produced in genetically engineered mammalian (Chinese hamster ovary) cells.
Hyperlink to the Product Information	Refer to Module 1.3.1 Product Information Refer to Prolia RMP v 31.0, 11-Jan-2023 Refer to Xgeva RMP v 36.0, 11-Dec-2020
Indication(s) (global)	Current: Not Applicable
	Proposed: Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures. In postmenopausal women

	Conexxence significantly reduces the risk of vertebral, non-vertebral and hip fractures. Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. In men with prostate cancer receiving hormone ablation, Conexxence significantly reduces the risk of vertebral fractures. Treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture.
Dosages	Current: Not Applicable
	Proposed: The recommended dose is 60 mg denosumab administered as a single subcutaneous (SC) injection once every 6 months (Q6M) into the thigh, abdomen or upper arm. Patients must be adequately supplemented with calcium and vitamin D.
Pharmaceutical form(s) and strengths	Current: Not applicable
	Proposed: - Solution for injection in pre-filled syringes. Each pre-filled syringe contains 60 mg of denosumab in 1 mL of solution (60 mg/mL).
Is/will the product be subject to additional monitoring?	Yes

Part II: Safety Specification

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

Module SI of the Conexxence RMP is in line with the reference medicinal product, Prolia®, solution for injection, Amgen, EU RMP version number 31.0, dated 11-Jan-2023.

SI.1 Summary of Epidemiology of Postmenopausal Osteoporosis (PMO)

Incidence

The incidence of osteoporosis in women aged > 50 years was 4,823 per million per year in Denmark (Vestergaard et al. 2005).

Prevalence

The prevalence of osteoporosis in women in the EU aged > 50 years was 22.1% in 2010, corresponding to approximately 22,100,000 women. Prevalence ranged from 19.3% in Cyprus to 23.4% in Italy. Prevalence increases with age, ranging from 6.3% in women aged 50 - 54 to 47.2% in women aged > 80 years (Hernlund et al. 2013).

Demographics of the population in the proposed indication and risk factors for the disease

All patients with PMO are women who have completed menopause. Most women with PMO are > 50 years of age and the incidence of PMO increases with age. Hormone ablation in women with breast cancer causes chemical menopause; these patients may be younger than 50 years of age. Women who have completed menopause are at risk for PMO. Risk factors for osteoporotic fracture include race (risk highest in those of European descent relative to Asian or African descent), lower bone mineral density (BMD), older age, history of previous fractures, parental history of hip fracture, current tobacco smoking, and high alcohol consumption (Cummings et al. 2006, Johnell et al. 2005, Kanis et al. 2001, Siris et al. 2004).

The main existing treatment options

- Calcium and vitamin D supplementation
- Weight-bearing and muscle-strengthening exercise
- Antiresorptive therapies such as bisphosphonates
- Selective estrogen receptor modulators
- Hormone replacement therapies
- Anabolic treatment: parathyroid hormone (PTH) analogs, PTH-related protein analog (abaloparatide), and strontium ranelate (the latter is both anabolic and anti-resorptive).

Natural history of the indicated condition in the untreated population, including mortality and morbidity

Lifetime risk of osteoporotic fracture in women is 40% to 50% (Dennison et al. 2006). Hip fractures often result in disability and loss of independence (Cree et al. 2000, Cummings and Melton 2002) and approximately 20% of women die within a year of hip fracture (Cooper et al. 1993, Johnell et al. 2004, Leibson et al. 2002). Hormone ablation therapy for women with breast cancer has been shown to be accompanied by increased bone loss (up to 3% per year at the lumbar spine and 2% per year at the total hip) and risk for fracture (11% to 49% increase) (Baum et al. 2003, Coates et al. 2007, Howell et al. 2005, Reid et al. 2008).

Important comorbidities

- Cardiovascular Disease (Bagger et al. 2007, Ensrud et al. 2010, Tankó et al. 2005);
- Malignancy (McGlynn et al. 2008, Olsson and Hägglund 1992, Persson et al. 1994);
- Infection (Dong et al. 2014, FDA 1997, Greenspan et al. 2007, Upala et al. 2016) .

In women with PMO, therapy for bone loss is generally administered in conjunction with calcium and vitamin D supplementation.

SI.2 Summary of Epidemiology of Male Osteoporosis (MOP)

Incidence

The incidence of male osteoporosis was 862 per million per year in Denmark (Vestergaard et al. 2005).

Prevalence

Prevalence of MOP has been reported at 17.7% in Denmark (Vestergaard et al. 2005) and 2.7% in the United Kingdom (Holt et al. 2002). In the Netherlands, prevalence was 12.1% for men ≥ 55 years of age, with the age-specific prevalence ranging from 15% in men aged 65 to 69 years to 36% in men aged > 85 years (Smith et al. 2004). North American prevalence tended to be lower (6.3% in Canada (Papaioannou et al. 2008) and 2% to 6% in the United States (Looker et al. 1997).

Demographics of the population in the proposed indication and risk factors for the disease

Compared with PMO, MOP occurs at a slightly older age, and the osteoporosis-related fracture incidence is lower. The consequences of MOP, however, are substantial because the associated fractures result in considerable morbidity and mortality.

Primary osteoporosis that results from decreased gonadal function contributes to most PMO and approximately half of MOP; the remainder of MOP is considered secondary due to conditions such as glucocorticoid (GC) use, excess alcohol use, and hyperparathyroidism (Cauley 2006, Ebeling 2008).

The Main Existing Treatment Options

- Calcium and vitamin D supplementation
- Weight-bearing and muscle-strengthening exercise
- Antiresorptive therapies such as bisphosphonates
- Anabolic treatment: PTH analogues.

Natural history of the indicated condition in the untreated population, including mortality and morbidity

Lifetime risk of osteoporosis-related fracture in men has been reported to be between 13% to 22% (Dennison et al. 2006). Post-hip fracture mortality in men is double that of women (Center et al. 1999, Kannegaard et al. 2010, Kiebzak et al. 2002, Piirtola et al. 2008) and the disability from fractures is high (Di Monaco et al. 2012, Poór et al. 1995).

Important comorbidities

- Cardiovascular disease (Szulc et al. 2009);
- Malignancy (Ji et al. 2012, McGlynn et al. 2008);
- Infection (Boonen et al. 2009, Figura et al. 2005, Kaufman et al. 2013, Orwoll et al. 2012).

In men with osteoporosis, pharmacologic therapy for bone loss is generally administered in conjunction with calcium and vitamin D supplementation.

SI.3 Summary of Epidemiology of Bone Loss Due to Hormone Ablation Therapy in Men with Prostate Cancer

Incidence

In Europe in 2006, it was estimated that > 340,000 men had prostate cancer with over 87,000 deaths (Ferlay et al. 2007). Rates in northern European countries tended to be higher than in southern European countries. Age-standardized incidence rates in Norway, Sweden, Finland, and Denmark were 133.2, 157.2, 149.7, and 80.3 events per 100,000 person-years, respectively, compared with 77.2, 108.4, 101.2, and 81.0 events per 100,000 person-years in Spain, Italy, Portugal, and Greece (Ferlay et al. 2007).

Prevalence

Prevalence of prostate cancer in 12 European countries (Netherlands, Poland, United Kingdom, Italy, Switzerland, Iceland, Norway, Germany, Scotland, Slovakia, Slovenia, and Sweden) in 2003 was 625 per 100,000 (Gatta et al. 2013).

Demographics of the population in the proposed indication and risk factors for the disease

Patients with prostate cancer are men, and the incidence of prostate cancer increases with age.

Hormone ablation in the form of androgen deprivation therapy (ADT) is frequently used as first-line, second-line, and adjuvant antineoplastic therapy for prostate cancer (Bolla et al. 2002,

Messing et al. 1999). Reductions in oestrogen and testosterone due to ADT increase risk of bone loss and fracture. Agents used for ADT include luteinizing hormone releasing hormone (LHRH) agonists (e.g., leuprorelin, buserelin, histrelin), LHRH antagonists (e.g., abarelix, cetrorelix, degarelix), steroidal antiandrogens (e.g., megestrol acetate, medroxyprogesterone acetate), and nonsteroidal antiandrogens (e.g., bicalutamide, flutamide).

The Main Existing Treatment Options

Only Prolia (denosumab 60 mg Q6M) is approved as treatment for bone loss associated with hormone ablation in men with prostate cancer.

Natural history of the indicated condition in the untreated population, including mortality and morbidity

The risk of osteoporotic fracture is increased by approximately 50% in men with prostate cancer who undergo hormone ablation (Shahinian et al. 2005). Risk of osteoporotic fracture increases at the hip, pelvis, extremities, and ribs, as compared with controls (Daniell 1997, Melton et al. 2003, Shahinian et al. 2005, Smith et al. 2005). The reported 1-year mortality rate after hip fracture in older men is 31% (Campion and Maricic 2003). Oefelein et al (2002) reported a negative correlation between fractures at any location and overall survival in men receiving ADT for prostate cancer (Oefelein et al. 2002).

Important comorbidities

- Cardiovascular disease (Alibhai et al. 2009, D'Amico et al. 2007, Keating et al. 2010, Keating et al. 2006, Li et al. 2012, Martín-Merino et al. 2011, Saigal et al. 2007);
- Malignancy (Liu et al. 2011, Thellenberg et al. 2003);
- Infection (Li et al. 2012).

In men with prostate cancer undergoing hormone ablation, therapy for bone loss is generally administered in conjunction with calcium and vitamin D supplementation.

SI.4 Summary of Epidemiology of Glucocorticoid-induced Osteoporosis

Incidence

Glucocorticoid use increases almost linearly with age, from 3.0% at 30 years of age to 3. 7% at 50 years, and up to 5.2% at 80 years of age as reported in a meta-analysis that included 42,500 men and women from 7 prospectively studied cohorts across Europe, Canada, the United States, and Australia (Kanis et al. 2004). In the European cohorts included in this meta-analysis, corticosteroid use was reported in 1.9% to 9.2% of women (average age between 64 to 80 years depending on the cohort) and 2.2% to 3.6% of men (average age 65 to 68 years) (Kanis et al. 2004). In the global longitudinal study of osteoporosis in women, which sampled women aged > 55 years from primary care practices in 10 countries, corticosteroid use was reported in 2.7% of women across Europe (Díez-Pérez et al. 2011). In population-based studies in the United Kingdom, between 0.5% to 0.9% of the population was reported to use oral corticosteroids (Fardet et al. 2011, van Staa et al. 2000, Walsh et al. 1996). Oral GCs are estimated to be used by 1.2% of the US population aged

> 20 years between 1999 and 2008, and 65% of the GC users reported usage > 90 days (Overman et al. 2013).

Prevalence

A population-based study of general practitioner records in the United Kingdom reported that 0.9% of the population aged 18 years or older used oral GCs. Prevalence of use increased with age from 0.2% among 20- to 29-year-olds to 2.5% among 70- to 79-year-olds. Long-term use (for 6 months or longer) was seen in 22% of the total population (van Staa et al. 2000). A study from Iceland reported that 0.7% of the population reported receiving long-term treatment with prednisolone (Gudbjornsson et al. 2002). The prevalence of fractures in patients receiving long-term GCs has been reported to be 30% to 50% (Weinstein 2011).

Demographics of the population in the proposed indication and risk factors for the disease

Long-term (90 days) GC therapy is mostly used in patients diagnosed with joint diseases (rheumatoid arthritis [RA], polymyalgia rheumatica [PMR], and connective tissue diseases), respiratory diseases (asthma and chronic obstructive pulmonary disease [COPD]), and chronic inflammatory bowel disease [IBD]) (Fardet et al. 2011, Saag 2003, van Staa et al. 2000).

Risk factors for glucocorticoid-induced osteoporosis (GIOP) include low body mass index, parental history of hip fracture, current smoking, >3 alcoholic drinks per day, higher daily GC dose, higher cumulative GC dose, intravenous pulse GC usage, and declining central BMD measurement that exceeds the least significant change (Grossman et al. 2010). Other risk factors include advancing age, underlying disease including RA, PMR, IBD, COPD, and transplantation, GC receptor genotype, and 11 beta-hydroxysteroid dehydrogenase isoenzymes (Weinstein 2011).

The Main Existing Treatment Options

Risedronate and zoledronic acid are approved for the prevention of glucocorticoid-induced osteoporosis (GIOP). Alendronate, risedronate, zoledronic acid, and teriparatide are approved for the treatment of GIOP.

Natural history of the indicated condition in the untreated population, including mortality and morbidity

Complications of long-term GC use include osteoporosis (associated with ~ 2-fold increased risk of fractures (Kanis et al. 2004)), Cushing's syndrome (Gudbjornsson et al. 2002), adrenal suppression, hyperglycemia and diabetes, cardiovascular disease and dyslipidemia, cataracts and glaucoma, dermatological and gastrointestinal events including acute pancreatitis, psychiatric disturbances, and immunosuppression, infectious complications, skin cancer, and non-Hodgkin lymphoma (Liu et al. 2013, Sørensen et al. 2004, Stuck et al. 1989).

Treatment with GC > 5 mg/day was significantly associated with an increased mortality in Germany (Listing et al. 2015) and United Kingdom (Movahedi et al. 2016) RA patients, and the association was independent of disease activity. No association between GC use and mortality was found among COPD patients (Kew and Seniukovich 2014, Walters et al. 2014). No literature describing mortality related to GC use in patients with other common indications was identified.

In general, osteoporotic fractures decrease a patient's quality of life by increasing pain, medical costs, and morbidity (Kanis et al. 2007). Excess mortality occurred in both men and women after osteoporotic fractures (Center et al. 1999).

Important comorbidities

- Respiratory diseases (Feldstein et al. 2005, Mudano et al. 2001, van Staa et al. 2000, Walsh et al. 1996);
- Joint diseases (Feldstein et al. 2005, Mudano et al. 2001, van Staa et al. 2000, Walsh et al. 1996);
- Chronic IBDs: (Feldstein et al. 2005, Mudano et al. 2001, van Staa et al. 2000, Walsh et al. 1996);
- Other complications associated with GC use (e.g., Cushingoid features, skin cancer, non-Hodgkin's lymphoma, infectious complications, weight gain, cataracts) (Curtis et al. 2006, Gabriel et al. 1997, Huscher et al. 2008, Proven et al. 2003, Sørensen et al. 2004, Stuck et al. 1989).

In men and women with GIOP, therapy for bone loss is generally administered in conjunction with calcium and vitamin D supplementation.

The most common indications for which oral corticosteroids are prescribed include RA (Mudano et al. 2001, Walsh et al. 1996) and COPD (Feldstein et al. 2005, Gudbjornsson et al. 2002, van Staa et al. 2000). Medications used to treat RA include traditional disease modifying antirheumatic drugs such as hydroxychloroquine; leflunomide, methotrexate, and sulfasalazine; tumour necrosis factor inhibitor biologics (such as adalimumab, certolizumab pegol, etanercept, golimumab, or infliximab); non-tumour necrosis factor biologics (such as abatacept, rituximab, ortocilizumab) and tofacitinib (Alamanos et al. 2006, Singh et al. 2016). The percentage of RA patients enrolled in a multinational observational study from 2011 to 2012 treated with methotrexate at baseline ranged from 79% in Italy to 98% in the United Kingdom, and for any biologic therapy from 3% in Uruguay to 77% in the United Kingdom (Dougados et al. 2014).

Bronchodilator drugs are regularly used to treat COPD, including short-acting beta2-agonists (such as fenoterol, salbutamol [albuterol], terbutaline) or long-acting beta2-agonists (formoterol, salmeterol), short-acting anticholinergics such as ipratropium bromide, oxitropium bromide or long-acting anticholinergics (tiotropium), and methylxanthines (such as aminophylline, theophylline) (National Clinical Guideline 2010, Rabe et al. 2007). In a prevalent sample of COPD patients in the United Kingdom (2013), the majority of patients were treated with combination therapy (56%), the most common combination being long-acting anticholinergics, long-acting beta agonists and inhaled corticosteroids (29%) or long-acting beta agonists and inhaled corticosteroids only (20%) (Raluy-Callado et al. 2015).

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

The similarity of Conexxence with the currently approved and marketed reference product, Prolia (denosumab) has been investigated in a series of physicochemical and in vitro pharmacodynamic

studies. Based on already available data, the analytical similarity between Conexxence and denosumab in terms of molecular structure and biological activity has been demonstrated. Therefore, the risk for unexpected off-target toxicity is considered negligible. Taking together these considerations, Fresenius Kabi does not plan to conduct comparative repeat-dose toxicity studies or other additional nonclinical safety studies (including genotoxicity, carcinogenicity, reproductive and developmental toxicity, or local tolerance studies) with Conexxence.

Key safety findings from non-clinical studies and relevance to human usage (in line with the reference product, Amgen Prolia RMP v31.0, 2023).

Toxicity

Reproductive Toxicity

At area under the curve (AUC) exposures up to 100-fold higher than the human exposure (every 6 months [Q6M]), denosumab showed no evidence of impaired fertility in cynomolgus monkeys. In a study of cynomolgus monkeys dosed with denosumab during the period equivalent to the first trimester at AUC exposures up to 99-fold higher than the human dose (Q6M), there was no evidence of maternal or foetal harm. In this study, foetal lymph nodes were not examined. In cynomolgus monkeys dosed with denosumab throughout pregnancy, effects including stillbirths and increased postnatal mortality; abnormal bone growth, reduced haematopoiesis, and tooth malalignment; absence of peripheral lymph nodes; and decreased neonatal growth were noted at AUC exposures up to 119-fold higher than the human exposure (60 mg Q6M). There was no evidence of maternal harm prior to labour; adverse maternal effects occurred infrequently during labour. Maternal mammary gland development was normal. In genetically engineered mice in which RANKL has been turned off by gene removal (a "knockout mouse"), studies suggest absence of RANKL during pregnancy may interfere with maturation of the mammary gland leading to impaired lactation post-partum.

Relevance to human usage: Monkeys exposed to denosumab in utero phenotypically resembled human infants with osteoclast-poor osteopetrosis due to inactivating mutations of RANK or RANKL Therefore, denosumab is not recommended for use in pregnant women. Women should be advised not to become pregnant during and for at least 5 months after treatment with denosumab.

It is not known if denosumab is excreted in human milk. Because denosumab has the potential to cause adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug. Use in pregnant and lactating women is not considered a safety concern in this RMP. These populations are not included in the intended indications. In addition, risk minimization via product labelling to avoid pregnancy and breastfeeding is in place.

Developmental Toxicity

In neonatal rats, administration of the RANKL inhibitor osteoprotegerin (OPG) bound to Fc (OPG-Fc) resulted in reduced weight gain, reduced bone growth, and inhibited tooth eruption. Despite reductions in bone growth, most bone strength parameters were increased with these treatments. In neonatal cynomolgus monkeys exposed in utero to denosumab at 50 mg/kg, there was increased postnatal mortality; abnormal bone growth resulting in reduced bone strength, reduced haematopoiesis and tooth malalignment; absence of peripheral lymph nodes; and decreased neonatal growth. Following a recovery period from birth out to 6 months of age, the effects on

bone generally returned to normal; there were no adverse effects on tooth eruption; and minimal to moderate mineralization in multiple tissues was seen in 1 recovery animal.

Adolescent cynomolgus monkeys who received doses of denosumab 150 times the expected clinical exposure had enlargement of epiphyseal growth plates with decreased removal of cartilage matrix in this area, considered to be consistent with the pharmacological activity of denosumab.

Relevance to human usage:
Treatment with denosumab may inhibit eruption of dentition in paediatric patients and may impair bone growth in paediatric patients with open growth plates. Denosumab is not approved for use in paediatric patients and should not be used in paediatric patients. Risk minimization is in place via product labelling with respect to use in paediatric patients.

Safety Pharmacology

Not applicable.

Other toxicity-related

Not applicable.

Part II: Module SIII - Clinical trial exposure

Overview of Clinical Studies used for FKS518 Exposure

The clinical studies used to calculate patient exposure to FKS518 (denosumab) as of 03-Dec-2023 are the following:

- FKS518-001 (LUMIADE-1): A Double-blind, Randomized, 2-Arm, Single-dose, Parallel-group Study in Healthy Subjects to Compare the Pharmacokinetics, Pharmacodynamics, and Immunogenicity of FKS518 – Proposed Biosimilar to Denosumab with Prolia® (Lumiade-1 Study);
- FKS518-002 (LUMIADE-3): A Double-blind, Randomized, Multicentre, Multiple-dose, 2-arm, Parallel-group Study to Evaluate Efficacy, Pharmacodynamics, Safety, and Immunogenicity of FKS518 – Proposed Biosimilar to Denosumab with Prolia® in Postmenopausal Women with Osteoporosis (LUMIADE-3 Study).

Overview of Exposure Tables

The following tables present cumulative patient exposure per study, age, gender, and race. The number presented here are reflecting the number of patients who received at least one dose of FKS518.

Table 1 Exposure to FKS518 per study

Study Identifier	Treatment Groups	Number of subjects
FKS518-001	60 MG SC FKS518	107
FKS518-002	60 MG SC denosumab Core	277
	60 MG SC denosumab Transition	124
	Total	**508**

Table 2 Patient exposure to FKS518 by age group and by gender

Study Identifier	Treatment Groups	Age Group (Years)	Male n (%)	Female n (%)	Total n
FKS518-001	60 MG SC FKS518	28-55	107	0	107
FKS518-002	60 MG SC denosumab	55 - <65	0	183	183
		65 - 85	0	218	218
	Total		**107**	**401**	**508**

Table 3 Patient exposure to FKS518 by race

Race Group	Study Identifier	Number of Subjects
White	FKS518-001	107
	FKS518-002	401
	Total	**508**
Black or African American	FKS518-001	0
	FKS518-002	0
	Total	**0**
Asian	FKS518-001	0
	FKS518-002	0
	Total	**0**
American Indian or Alaska Native	FKS518-001	0
	FKS518-002	0
	Total	**0**
Native Hawaiian or Other Pacific Islander	FKS518-001	0
	FKS518-002	0
	Total	**0**
Other	FKS518-001	0
	FKS518-002	0
	Total	**0**
Not Reported	FKS518-001	0
	FKS518-002	0
	Total	**0**

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

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

Table 4 Important Exclusion Criteria in Pivotal Studies in the Development Program (in line with reference product, Amgen Prolia RMP v31.0, 2023)

Criterion	Reason for exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Hypocalcaemia	Hypocalcemia must be corrected by adequate intake of calcium and vitamin D before initiating therapy. Patients receiving denosumab must have adequate intake of calcium and vitamin D.	No	It is a contraindication in the Summary of Product Characteristics (SmPC).
Hypersensitivity to the active substance or to any of the excipients	Patients who are hypersensitive to denosumab or to any of the excipients should not receive denosumab.	No	It is a contraindication in the SmPC.
Bone mineral density (BMD) T-score < -4.0	It was considered unethical to enrol subjects with a T-score < -4.0 in Amgen's placebo-controlled studies when approved therapies were available, because these subjects would remain untreated for 3 years if randomized to the placebo group.	No	The safety and efficacy of denosumab is not expected to differ in subjects with lower BMD T-scores. In subgroup analyses by baseline lumbar spine and total hip T-score for the range of T-scores enrolled in the Amgen's large pivotal PMO study, denosumab was effective in each subgroup. Therefore, no special dosing recommendations for patients with BMD T-scores < -4.0 are considered necessary. Furthermore, subjects with BMD T-scores < -4.0 were not excluded from the Amgen's

Criterion	Reason for exclusion	Is it to be included as missing information? (Yes/No)	Rationale
			pivotal study in the GIOP population because the study was active-controlled (risedronate).
Other bone diseases	Patients with other bone diseases such as rheumatoid arthritis (RA), osteogenesis imperfecta (OI), and Paget's disease were excluded from the Amgen's pivotal osteoporosis studies because other bone diseases could confound the efficacy results.	No	Denosumab is not indicated for use in these other patient populations. However, subjects with RA were not excluded from the Amgen's pivotal study in the GIOP population, because RA is a common indication for glucocorticoid (GC) use.
Previous bisphosphonate treatment	Subjects with previous bisphosphonate treatment were excluded from Amgen's pivotal osteoporosis studies in accordance with regulatory guidance to demonstrate fracture benefit in a PMO population. Because bisphosphonates incorporate into bone and long-term use of bisphosphonates is associated with continued effects of the drug after treatment is stopped, it was deemed most appropriate to exclude previous bisphosphonate treatment.	No	In a double-blind, alendronate-controlled Amgen's study, in postmenopausal women with low BMD who had received bisphosphonates for at least 6 months preceding study entry, safety results were similar in the denosumab and alendronate treatment groups. In addition, 3 other Amgen's studies evaluated the effects of denosumab and a bisphosphonate (risedronate, ibandronate, or zoledronic acid, respectively) in postmenopausal women transitioning from previous bisphosphonate therapy.

Criterion	Reason for exclusion	Is it to be included as missing information? (Yes/No)	Rationale
			There were no new safety findings in these studies.
Evidence of distant metastases	Subjects with distant metastases have been evaluated in other clinical studies of denosumab using a different dose and schedule (up to 120 mg monthly).	No	An indication in this patient population was not sought for denosumab 60 mg. Amgen XGEVA (denosumab 120 mg) is approved for prevention of skeletal-related events in adults with bone metastases from solid tumours; thus, safety in this population is well documented.
Serum creatinine > 2.0 mg/dL	Treatment with antiresorptive agents reduces the ability to mobilize calcium from bone; thus, hypocalcaemia could be exacerbated in patients with renal impairment	No	One of Amgen's studies demonstrated that renal impairment does not affect the pharmacokinetics of denosumab; therefore, no dose adjustments are required in patients with impaired renal function. Recommendations for adequate intake of calcium and vitamin D in all patients, and recommendations for monitoring of serum calcium in patients predisposed to hypocalcaemia, have been included in the SmPC. No other special dosing recommendations are considered necessary for subjects with renal impairment.

Criterion	Reason for exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Subjects who are pregnant or breastfeeding, or planning to become pregnant	Adequate and well-controlled studies with denosumab have not been conducted in pregnant women due to the potential risk to the foetus. It is not known whether denosumab is transferred into human milk.	No	These populations are not included in the intended indications. Risk minimization via product labelling instructing patients to avoid pregnancy and breast feeding is in place. No additional pharmacovigilance activities or additional risk minimization are warranted.

SIV.2 Limitations to detect adverse reactions in clinical trials development program

The clinical development program 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 program

Table 5 Exposure of special populations included or not in clinical trial development program

Type of special population	Exposure
Pregnant women and breastfeeding women	The FKS518 clinical development program included postmenopausal women above 55 years of age, at screening. One partner pregnancy was reported. In the Originator's clinical development program (Amgen Prolia EU-RMP v31.0, 2023) there were 8 pregnancies reported; no cases of lactation were reported.
Patients with Relevant Comorbidities	

Type of special population	Exposure
Patients with hepatic impairment	No specific exclusion criteria were considered in the FKS518 clinical development program. The Originator's clinical development program (Amgen Prolia EU-RMP v31.0, 2023) did not included patients with hepatic impairment.
Patients with renal impairment	Excluded from the FKS518 clinical development program. The Originator's clinical development program (Amgen Prolia EU-RMP v31.0, 2023) did not specifically excluded subjects with renal impairment from Prolia clinical studies. A total of 6802 subjects (26501.2 subject-years), 3942 subjects (15866.9 subject-years), 84 subjects (273.8 subject-years), and 2 subjects (7.1 subject-years) with mild, moderate, or severe renal impairment, or kidney failure, respectively, were exposed to Prolia in the clinical development program.
Patients with cardiovascular impairment	No specific exclusion criteria were considered in the FKS518 clinical development program. In a large pivotal PMO study of the Originator's clinical development program (Amgen Prolia EU-RMP v31.0, 2023), a substudy was conducted in 2363 subjects with high cardiovascular risk.
Immunocompromised patients	Excluded from the FKS518 clinical development program. The Originator's clinical development program (Amgen Prolia EU-RMP v31.0, 2023) did not consider specific exclusions with exception of human immunodeficiency virus (HIV) positive patients.
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program of both FKS518 and Prolia.
Subpopulations carrying relevant genetic polymorphisms	No specific exclusions in both FKS518 and Prolia clinical development programs.

Type of special population	Exposure
Population with relevant different ethnic origin	Not included in the clinical development program of FKS518. The Originator's clinical development program (Amgen Prolia EU-RMP v31.0, 2023) included a total of 12736 subjects (48154.6 subject-years), 146 subjects (477.7 subject-years), 708 subjects (2742.7 subject-years), and 287 subjects (429.8 subject-years) of white, black or African American, Hispanic or Latino, or Asian race/ethnicity, respectively, were exposed to Prolia in the clinical development program. In pivotal studies, 451 of 4910 subjects who received denosumab belonged to an ethnic or racial minority (PMO: 321/4050; HALT 130/860).
Other	
Paediatric patients	Not included in the clinical development program of FKS518. The Originator's clinical development program (Amgen Prolia EU-RMP v31.0, 2023) included: - Male: A total of 17 subjects (49.9 subject-years), 29 subjects (91.2 subject-years), and 47 subjects (145.9 subject-years) aged 2 to 6 years, 7 to 10 years, and 11 to 17 years, respectively, were exposed to Prolia, in the clinical development program. - Female: A total of 22 subjects (66.4 subject-years), 26 subjects (79.7 subject-years), and 33 subjects (93.1 subject-years) aged 2 to 6 years, 7 to 10 years, and 11 to 17 years, respectively, were exposed to Prolia, in the clinical development program.

Type of special population	Exposure
Geriatric patients	Not included in the FKS518-001 study but considered for inclusion in the FKS518-002 study up to 85 years of age. The Originator's clinical development program (Amgen Prolia EU-RMP v31.0, 2023) included: - Male: A total of 688 subjects (1428.9 subject-years), 607 subjects (1372.3 subject-years), and 68 subjects (168.5 subject-years) aged 65 to 74 years, 75 to 84 years, and >85 years, respectively, were exposed to Prolia, in the clinical development program. - Female: A total of 6123 subjects (28041.0 subject-years), 2505 subjects (10279.6 subject-years), and 119 subjects (301.7 subject-years) aged 65 to 74 years, 75 to 84 years, and ≥85 years, respectively, were exposed to Prolia, in the clinical development program.
Patients with BMD T-score < -4.0	Not included in the clinical development program of FKS518. The Originator's clinical development program (Amgen Prolia EU-RMP v31.0, 2023) did not explicitly excluded subjects with BMD T-score < -4.0 from Prolia clinical studies, except one study.

Part II: Module SV - Post-authorization experience

Not applicable. Conexxence (denosumab 60 mg) is not yet marketed.

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

Potential for Misuse for Illegal Purposes

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

Part II: Module SVII - Identified and potential risks

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

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

Not applicable.

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

Following a comprehensive review of the FKS518 safety data and based on clinical experience with the reference product Amgen's Prolia (denosumab), the following are considered important risks:

- Important identified risks:

  1. Hypocalcaemia;
  2. Skin infection leading to hospitalization;
  3. Osteonecrosis of the jaw;
  4. Hypersensitivity reactions;
  5. Atypical Femoral Fracture;
  6. Hypercalcemia in paediatric patients receiving denosumab and after treatment discontinuation.

- Important potential risks:

  1. Fracture healing complications;
  2. Infection;
  3. Cardiovascular events;
  4. Malignancy.

Further details on the safety concerns are provided in section SVII.3.1.

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

Not applicable.

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

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

Table 6. Details of important identified and potential risks of denosumab

Important identified risk **Hypocalcaemia**	
Potential mechanism	Denosumab inhibits osteoclast bone resorption, thereby decreasing the release of calcium from bone into the bloodstream.
Evidence source(s) and strength of evidence	The source of information is clinical/safety and postmarketing data of the reference product Amgen Prolia (EU-RMP v31.0, 2023) and medical literature.
Characterization of the risk	*Frequency* In Amgen's pooled pivotal studies for PMO and hormone ablation therapy (HALT) subject incidence of hypocalcaemia adverse events was < 0.1% in denosumab-treated subjects and 0.1% in placebo-treated subjects. The incidence of hypocalcaemia adverse events was lower in denosumab-treated subjects than in placebo-treated subjects; thus, 95% CIs were not calculated. In the 24-month final analysis of the GIOP study, subject incidence of hypocalcaemia adverse events was 0.3% in the denosumab group; there were no adverse events of hypocalcaemia in the risedronate group thus, 95% CIs were not calculated. *Severity* While most hypocalcaemia events are mild to moderate in severity, severe events have occurred. *Reversibility* Hypocalcaemia is reversible when treated with oral calcium and vitamin D supplementation. In severe cases, IV calcium supplementation may be required. *Long-term outcomes* No long-term complications are anticipated for properly treated hypocalcaemia.

	Impact on quality of life For severe symptomatic hypocalcaemia, patients may be hospitalized for treatment. Generally, patients recover when their hypocalcaemia is treated.
Risk group or risk factors	Risk factors include severe renal impairment and hyperphosphatemia. Other risks factors may include a history of hypoparathyroidism, PTH resistance, vitamin D deficiency or resistance, thyroid surgery, parathyroid surgery, malabsorption syndromes, excision of small intestine, severe renal impairment (CrCl<30 mL/min), dialysis, and some medications (Finkelstein 2001).
Preventability	Pre-existing hypocalcaemia should be corrected by adequate intake of calcium and vitamin D before initiating therapy, and supplementation with calcium and vitamin D is important during therapy in all patients receiving denosumab. Clinical monitoring of calcium levels is recommended during treatment, especially in those with renal impairment.
Impact on the risk-benefit balance of the product	The risk of hypocalcaemia has been considered in the product benefit-risk assessment. In light of the product labelling addressing this risk, the overall benefit-risk balance is considered to be positive.
Public health impact	Significant public health impact is not expected as this risk is preventable and treatable with the appropriate risk mitigating measures communicated clearly in the SmPC.
Important identified risk **Skin infection leading to hospitalization**	
Potential mechanism	Keratinocytes can express RANKL and blocking RANKL in mice decreased the number of regulatory T-cells in skin, leading to an increased inflammatory response (Loser et al. 2006, Yamaguchi and Sakaguchi 2006).
Evidence source(s) and strength of evidence	The source of information is clinical/safety data of the reference product Amgen Prolia (EU-RMP v31.0, 2023) and medical literature.
Characterization of the risk	*Frequency* In Amgen's pooled PMO/HALT pivotal studies, subject incidence of skin infection was 1.4% with denosumab and 1.3% with placebo; the hazard ratio (HR) was 1.09 (95% CI: 0. 78, 1.53). Subject incidence of serious adverse events of skin infection was 0.4% with denosumab and 0.2% with placebo (HR [95% CI] = 2.55 [1.13, 5.76]). In the 24-month final analysis of the GIOP study, subject incidence of adverse events of skin infection was 1.8% with denosumab and 0.5% with risedronate; the HR was 3.62 (95% CI = 0.75,

	17.42). Subject incidence of serious adverse events of skin infection was 0.5% in both the denosumab and risedronate groups (HR [95% CI] = 1.03 [0.15, 7.34]). *Severity* Serious adverse events of skin infection were mostly severe in intensity. *Reversibility* These events typically resolved with administration of antibiotics. *Long-term outcomes* No long-term complications are anticipated for properly treated patients who are hospitalized due to skin infections. *Impact on quality of life* Requires a hospital stay; patients generally recover with antibiotic treatment.
Risk group or risk factors	Risk factors for infection in general include increasing age, immunosuppression associated with cancer, diabetes, HIV/acquired immune deficiency syndrome (AIDS), immunosuppressant drugs (e.g., corticosteroids, arthritis medications, and chemotherapy drugs), substance abuse, and malnutrition. Risk factors for skin infection in older patients include skin wounds, peripheral vascular disease, eczema/dermatitis, and venous stasis disorders.
Preventability	No preventive measures are known.
Impact on the risk-benefit balance of the product	The risk of skin infection leading to hospitalisation has been considered in the product benefit-risk assessment. In light of the product labelling addressing this risk, the overall benefit-risk balance is considered to be positive.
Public health impact	Since frequency of skin infection leading to hospitalisation is relatively low, absolute difference between denosumab and placebo groups is relatively small, and the adverse events can be effectively treated by antibiotics, the negative impact to public health is relatively small.
Important identified risk **Osteonecrosis of the Jaw**	
Potential mechanism	Osteonecrosis of the jaw (ONJ) appears to be multifactorial and multiple hypotheses have been postulated and have included factors such as inhibition of bone remodelling, infection and inflammation, inhibition of angiogenesis, soft tissue toxicity, altered immunity and genetic predisposition. As yet, evidence supporting these hypotheses has been variable and little is

	understood in how these multiple pathways might interact (Aghaloo et al. 2015, Fassio et al. 2017).
Evidence source(s) and strength of evidence	The source of information is clinical/safety data of the reference product Amgen Prolia (EU-RMP v31.0, 2023) and medical literature.
Characterization of the risk	*Frequency* No cases of ONJ have been reported in Amgen's placebo-controlled studies (although cases were reported in open-label extensions to the pivotal PMO study and a HALT study); thus, 95% CIs were not calculated. No cases of ONJ were reported in the GIOP study. Overall, across the Amgen-sponsored clinical development program for Prolia, positively adjudicated ONJ cases have been reported rarely (18 ONJ cases in 23,552 subjects, 0.076%) in subjects cumulatively exposed to denosumab (60 mg) clinical studies. *Severity* Most events leading to adjudication as ONJ were assessed as moderate in severity. Mild and severe events were also reported (Amgen Prolia EU-RMP v31.0, 2023). *Reversibility* In general, ONJ events are clinically reversible with supportive care, antibiotics; however, surgical treatment may be required. *Long-term outcomes* No data on long-term outcomes are available. *Impact on Quality of Life* Discomfort associated with ONJ lesions and/or with more extensive treatments may impact patient wellbeing via decreased oral intake (e.g., decreased hydration and decreased nutritional intake).
Risk group or risk factors	Risk factors include duration of exposure to denosumab, prior bisphosphonate use (particularly for extended periods of time), older age, periodontal disease, dentoalveolar surgery, trauma from poorly fitting dentures, malignancy, chemotherapy, corticosteroids, smoking, systemic or regional infection, immune-compromised state predisposing to increased risk of infection, hypercoagulable state secondary to underlying malignancy, and vascular insufficiency due to thrombosis (Mehrotra and Ruggiero 2006, Ruggiero et al. 2006).
Preventability	A dental examination with appropriate preventive dentistry is recommended prior to treatment with denosumab, especially in patients with risk factors.

	While on treatment, patients should avoid invasive dental procedures where possible. Patients who are suspected of having or who develop ONJ while on denosumab should receive care by a dentist or an oral surgeon. In patients who develop ONJ during treatment with denosumab, a temporary interruption of treatment should be considered based on individual risk/benefit assessment until the condition resolves.
Impact on the risk-benefit balance of the product	The risk of ONJ events has been considered in the product benefit-risk assessment. In light of the product labelling and a patient reminder card that has been proposed to minimize this risk, the overall benefit-risk balance is considered to be positive.
Public health impact	Significant public health impact is not expected with denosumab, as the event is rare and the actions taken to minimize the likelihood of developing ONJ are described in the prescribing information.
Important identified risk **Hypersensitivity reactions**	
Potential mechanism	Two types of allergic reactions, immunoglobulin E (IgE)- and non-lgE-mediated, appear to be related to monoclonal antibody administration. The lgE-mediated reactions can cause both wheal and flare reactions at the injection site, but may also be associated with urticaria and anaphylaxis. The mechanism of non-lgE reactions is unclear.
Evidence source(s) and strength of evidence	The source of information is postmarketing data of the reference product Amgen Prolia (EU-RMP v31.0, 2023).
Characterization of the risk	*Frequency* In Amgen's pooled PMO/HALT pivotal studies, subject incidence of hypersensitivity and drug hypersensitivity was 1.0% in denosumab-treated subjects and 0.8% in placebo-treated subjects; HR = 1.26 (95% CI: 0.83, 1.90). Subject incidence of potential clinical consequences of hypersensitivity was 1.3% in both treatment groups; HR = 0.94 (95% CI: 0.66, 1.33). In the 24-month final analysis of the GIOP study, subject incidence of adverse events potentially associated with hypersensitivity was 6.3% in denosumab-treated subjects and 4.7% in risedronate-treated subjects (HR [95% CI] = 1.41 [0.77, 2.59]). *Severity* Most hypersensitivity reactions are mild to moderate in severity; severe events have occurred. *Reversibility*

	Hypersensitivity reactions are generally reversible with discontinuation of the medication, though treatment may be required. *Long-term outcomes* No long-term complications are anticipated for properly treated hypersensitivity reactions. *Impact on Quality of Life* For severe hypersensitivity reactions, patients may be treated in the emergency room and/or hospitalized for treatment. Generally, patients recover when denosumab is discontinued with or without additional treatment.
Risk group or risk factors	Known hypersensitivity to denosumab and any of its excipients.
Preventability	No data are available on potential measures to prevent hypersensitivity reactions to denosumab. The appropriate contraindication information on hypersensitivity to denosumab and any of its excipients is included in the SmPC.
Impact on the risk-benefit balance of the product	The risk of hypersensitivity reactions has been considered in the product benefit-risk assessment. In light of the product labelling addressing this risk, the overall benefit-risk balance is considered to be positive.
Public health impact	No significant public health impact is expected as reports of severe events (e.g., anaphylaxis) are rare.
Important identified risk **Atypical femoral fracture**	
Potential mechanism	Prolonged suppression of bone turnover may be associated with increased risk of atypical femoral fracture (AFF), but the pathogenesis remains unclear and causes of AFF are likely multifactorial. Based on nonclinical studies of bisphosphonates, collagen cross-linking and maturation, accumulation of microdamage and advanced glycation end products, mineralization, remodelling, vascularity, and angiogenesis lend biologic plausibility to a potential association between these effects and AFF (Ismail et al. 2018, Shane et al. 2010).
Evidence source(s) and strength of evidence	The source of information is clinical/safety data of the reference product Amgen Prolia (EU-RMP v31.0, 2023) and medical literature.

Characterization of the risk	*Frequency* No cases of confirmed AFF have been reported in placebo-controlled studies; thus, 95% CIs were not calculated. In the GIOP study, subject incidence of confirmed AFF was 0.3% (1 event) in the denosumab group; there were no adverse events of AFF in the risedronate group thus, 95% CIs were not calculated. Overall, adjudicated-positive cases of AFF have been reported rarely (5 of 23,280 subjects, 0.021%) in subjects exposed to denosumab (60 mg) in clinical studies. *Severity* Atypical femoral fracture is a medically important adverse event that generally requires significant medical interventions such as surgery and ongoing monitoring to mitigate risk for and severity of contralateral fractures. The few events from Amgen's Prolia studies leading to adjudication of AFF were considered as severe in intensity. *Reversibility* Atypical femoral fracture is generally treatable with surgical intervention. It is unknown if the pathophysiological mechanism(s) contributing to the development of AFF are reversible after treatment is discontinued. *Long-term outcomes* No data on long-term outcomes are available. *Impact on Quality of Life* As with other femur fractures, AFF can cause short-term or long-term disability. Some data suggests that healing of AFF may be more prolonged than a typical femoral fracture (Bubbear 2016, Unnanuntana et al. 2013).
Risk group or risk factors	Long-term antiresorptive treatment has been associated with AFF. Corticosteroids have also been reported in the literature to potentially be associated with AFF (Giusti et al. 2011, Meier et al. 2012). Atypical femoral fractures have also been reported in patients with certain comorbid conditions (e.g., vitamin D deficiency, RA, hypophosphatasia) and with use of bisphosphonates, glucocorticoids, and proton pump inhibitors (Shane et al. 2010).
Preventability	No data are currently available on potential measures to prevent AFF. Patients using long-term antiresorptives may experience pain over the femur, which requires radiological examination if atypical fracture is suspected.
Impact on the risk-benefit	The risk of atypical femoral fracture has been considered in the product benefit-risk assessment. In light of the product labelling addressing this risk, the overall benefit-risk balance is considered to be positive.

balance of the product	
Public health impact	Based on the infrequency of AFF in patients treated with denosumab, no significant additional public health impact is expected.
Important identified risk **Hypercalcemia in paediatric patients receiving denosumab and after treatment discontinuation**	
Potential mechanism	The exact mechanism of hypercalcemia occurring in paediatric patients both during the dosing interval and following discontinuation is not certain but may be a consequence of the following, alone, or in combination: • Hypercalcemia may result from rapid resorption of retained primary spongiosa in a skeleton with active endochondral ossification. The rate of endochondral ossification and duration of exposure to denosumab would determine the amount of accumulated primary spongiosa that could influence the magnitude of resorptive response (mechanostat-driven) and release of calcium from resorbing bone matrix via an autocrine/paracrine mechanism. • The magnitude of the resorptive response following treatment and withdrawal in the immature skeleton could be dictated by the normal high rate of bone turnover in individuals with growing skeletons. • The response of the osteoclast lineage to loss of inhibition of osteoclastogenesis may be intrinsically more robust in individuals with growing skeletons. The increased skeletal metabolism related to bone modelling and growth in children is therefore likely to impact the frequency of hypercalcemia occurring both between the dosing interval and following discontinuation.
Evidence source(s) and strength of evidence	The source of information is clinical/safety and postmarketing data of the reference product Amgen Prolia (EU-RMP v31.0, 2023).
Characterization of the risk	*Frequency* In Amgen's completed paediatric OI studies, during the Q6M dosing regimen, hypercalcemia was reported for 29 subjects (19.0%). All these events were nonserious. During the every 3 months (Q3M) dosing regimen and following denosumab discontinuation, hypercalcemia was reported for 22 subjects (36.7%). Serious adverse events of hypercalcemia were reported for 8 subjects (13.3%).

	Severity Most subjects in the Amgen's paediatric OI study receiving the Q3M dosing regimen who had hypercalcemia events experienced mild events. Grade ≥3 hypercalcemia was reported for 10 subjects (16.7%). Grade 4 (life-threatening) hypercalcemia was reported for 4 subjects (6.7%). *Reversibility* Hypercalcemia is reversible when treated. In severe cases, use of rescue medications may be required. *Long-term outcomes* No long-term adverse effects are anticipated for properly treated hypercalcemia. *Impact on Quality of Life* Paediatric patients may present with severe hypercalcemia requiring hospitalization. Generally, patients recover when the hypercalcemia is treated.
Risk group or risk factors	Paediatric patients with growing skeletons and high bone turnover disease states (such as OI).
Preventability	Denosumab is not indicated in paediatric patients (age < 18 years) and should not be used in paediatric patients. If used in a clinical trial setting, monitoring for signs and symptoms and periodic serum calcium is advisable.
Impact on the risk-benefit balance of the product	The benefit-risk profile of denosumab is not favourable in the paediatric patient population.
Public health impact	Significant public health impact is not expected as this risk is preventable with the appropriate risk mitigating measures communicated clearly in the SmPC.
Important potential risk **Fracture healing complications**	
Potential mechanism	Because denosumab directly suppresses bone resorption and (indirectly) bone formation, it has the theoretical potential to delay fracture healing.
Evidence source(s) and	This is a theoretical risk based on the mechanism of action (Amgen Prolia EU-RMP v31.0, 2023).

strength of evidence	
Characterization of the risk	*Frequency* Of the subjects who had nonvertebral fractures in the large Amgen's pivotal PMO study, fracture healing complications (delayed healing or non-union) were reported in 2 of 386 subjects in the denosumab group (0.5%) and 5 of 465 subjects (1.1%) in the placebo group. Of the subjects who had nonvertebral fractures in the Amgen's pivotal study for HALT-breast cancer, fracture healing complications were reported in 0 of 8 subjects in the denosumab group and 1 of 8 subjects (12.5%) in the placebo group. Because of the low incidence of fracture healing complications, 95% CIs were not calculated. No fracture healing complications were reported in the Amgen's MOP and GIOP studies. *Severity* This risk has not been substantiated; however, impaired fracture healing could have significant impact on patient wellbeing. *Reversibility* This risk has not been substantiated; however, the effects of denosumab on osteoclasts are fully reversible. *Long-term outcomes* This risk has not been substantiated; however, no long-term impact would be anticipated based on reversibility. *Impact on Quality of Life* Fracture healing complications can cause short-term or long-term disability. Surgery may be required.
Risk group or risk factors	General risk factors for fracture healing complications are thought to include older age, diabetes, use of medications such as non-steroidal anti-inflammatory drugs and corticosteroids, smoking, excessive alcohol use, and poor nutrition (Gaston and Simpson 2007, Hernandez et al. 2012).
Preventability	No preventive measures are known.
Impact on the risk-benefit balance of the product	The potential risk of fracture healing complications has been considered in overall assessment supporting a positive benefit-risk profile.
Public health impact	No significant impact on public health is anticipated.

Important potential risk

Infection

Potential mechanism	RANK ligand is expressed on activated T and B cells and in the lymph nodes and some reports have described immune modulatory effects of RANKL inhibition. However, no clinically relevant effect of denosumab treatment was observed on peripheral blood immune cell subset profiles in studies in healthy elderly men, postmenopausal women, and postmenopausal women with low BMD. No evidence of a treatment effect of denosumab on immunoglobulin production was observed.
Evidence source(s) and strength of evidence	This is considered a potential risk based on theoretical concerns which has not been substantiated in the Amgen's extensive clinical study program or in the postmarketing experience (Amgen Prolia EU-RMP v31.0, 2023).
Characterization of the risk	*Frequency* Subject incidence[a] (%) / Hazard ratio (95% CI) Adverse events Placebo 50.6 — 0.98 (0.92, 1.03) Denosumab 50.1 Serious adverse events Placebo 3.4 — 1.25 (1.02, 1.53) Denosumab 4.3 Serious adverse events not including skin infection Placebo 3.3 — 1.18 (0.95, 1.45) Denosumab 3.9 Opportunistic infection Placebo 0.1 — - Denosumab 0.1 [a] Amgen's pooled pivotal studies for PMO and HALT and in prostate cancer and in breast cancer, Safety Analysis Set. In the 24-month final analysis of the GIOP study, subject incidence of infections was 36.3% with denosumab and 36.4% with risedronate; HR= 1.06 (0.84, 1.34). Subject incidence of serious adverse events of infection was 5.8% in the denosumab group and 6.5% in the risedronate group (HR [95% CI] = 0.95 [0.54, 1.68]). *Severity* The majority of reported events of infection were non serious. Serious adverse events were most commonly reported as severe in intensity. *Reversibility* Infections when treated appropriately are generally reversible.

	Long-term outcomes Infection generally responds to appropriate treatment and as such no long-term effects are anticipated. *Impact on Quality of Life* For severe infection, patients may be hospitalized for treatment. Generally, patients recover when their infection is treated.
Risk group or risk factors	Risk factors for infection in general include increasing age, immunosuppression associated with cancer, diabetes, HIV/AIDS, immunosuppressant drugs (e.g., corticosteroids, arthritis medications, and chemotherapy drugs), substance abuse, and malnutrition.
Preventability	No preventive measures are known.
Impact on the risk-benefit balance of the product	The potential risk of infection has been considered in the overall assessment which supports a positive benefit-risk profile in the indicated populations.
Public health impact	No significant public health impact is expected for this unsubstantiated risk as effective treatments are available.
Important potential risk **Cardiovascular events**	
Potential mechanism	Elevated levels of osteoprotegerin (OPG) have been associated with coronary artery disease in cross-sectional studies but this association has been contradicted by preclinical and epidemiological studies demonstrating that the lack of OPG or unopposed RANKL is associated with cardiac calcification. Because of these conflicting results and because denosumab inhibits RANKL, a theoretical concern for denosumab to affect progression of atherosclerosis exists.
Evidence source(s) and strength of evidence	This is a theoretical risk based on epidemiological data demonstrating elevated OPG in patients with cardiovascular disease (Amgen Prolia EU-RMP v31.0, 2023).
Characterization of the risk	*Frequency* In Amgen's pooled analysis of the large pivotal PMO study and the pivotal HALT-prostate study, the overall subject incidence of adjudicated-positive serious cardiovascular events was 5.8% with denosumab and 5.6% with placebo (HR [95% CI] = 1.00 [0.85, 1.19]). The subject incidence of positively adjudicated, pre-defined categories of serious cardiovascular event

was comparable between the treatment groups in the pooled analysis, as shown below:

Studies[a]	Subject incidence (%)	Hazard ratio (95% CI)
Acute coronary syndrome		
Placebo	1.4	0.96 (0.68, 1.35)
Denosumab	1.4	
Congestive heart failure		
Placebo	0.7	1.03 (0.64, 1.65)
Denosumab	0.8	
Stroke/transient ischemic attack		
Placebo	1.5	1.06 (0.77, 1.46)
Denosumab	1.7	
Arrhythmia		
Placebo	1.3	1.15 (0.82, 1.63)
Denosumab	1.5	
Other vascular disorders		
Placebo	0.9	1.13 (0.75, 1.71)
Denosumab	1.1	
Cardiovascular death		
Placebo	1.1	0.79 (0.52, 1.18)
Denosumab	0.9	

[a] Amgen's Safety Analysis Set.

During the placebo-controlled phase of the pivotal study for MOP, adverse events in the cardiac disorders system organ class (SOC) were reported in 8 (6.7%) denosumab-treated and 3 (2.5%) placebo-treated subjects (note: 2 events of angina tonsillitis in the denosumab group were incorrectly coded to the cardiac disorders adverse event category). The incidence of adverse events in the vascular disorders SOC was 5.0% in denosumab-treated and 6.7% in placebo-treated subjects.

In the GIOP study, adverse events in the cardiovascular disorders or vascular disorders SOC were reported in 65 (16.5%) denosumab-treated subjects and 53 (13.8%) risedronate-treated subjects (HR [95% CI] = 1.27 [0.88, 1.82]). Subject incidence of serious adverse events in the cardiovascular or vascular SOC was 3.8% on the denosumab group and 3.9% in the risedronate group.

In a retrospective cohort study assessing the incidence of cardiovascular and cerebrovascular events among postmenopausal women and men with osteoporosis treated with denosumab or zoledronic acid for up to 36 months of treatment, the unadjusted incidence rates of myocardial infarction, stroke, and myocardial infarction-stroke composite outcome were 0.23 to 0. 72 per 100 person-years. The differences in the unadjusted incidence rates of outcome between denosumab and zoledronic acid treatment groups were small (<0.1 risk difference).

	Severity This risk has not been substantiated; however, cardiovascular events may be severe/life-threatening. *Reversibility* This risk has not been substantiated; however, effects of denosumab to block RANKL are fully reversible. *Long-term outcomes* This risk has not been substantiated; however, cardiovascular events could impact patient long-term outcome. *Impact on Quality of Life* Cardiovascular disease varies greatly in severity. For severe disease, patients may be hospitalized for treatment and disability may occur.
Risk group or risk factors	The denosumab development program comprises studies of older subject populations (e.g., osteoporosis, cancer) that are likely to have a higher incidence of pre-existing cardiovascular conditions and, thus, a higher incidence of cardiovascular toxicities than that of the general population (Hak et al. 2000, Schulz et al. 2004). Risk factors for atherosclerosis include age, sex, ethnicity, family history, elevated lipid levels, cigarette smoking, hypertension, diabetes, and concomitant medications, including antipsychotic agents and COX-2 inhibitors (Murphy and Dargie 2007, Smith et al. 2004).
Preventability	No preventive measures are known.
Impact on the risk-benefit balance of the product	The potential risk of cardiovascular events has been considered in overall assessment supporting a positive benefit-risk profile.
Public health impact	Significant public health impact of Conexxence on cardiovascular disease severity or incidence is not anticipated.
Important potential risk **Malignancy**	
Potential mechanism	RANK ligand is expressed on activated T and B cells and in the lymph nodes and some reports have described immune modulatory effects of RANKL inhibition; however, in vitro studies of RANK and RANKL activity on a wide range of human tumour types provide no evidence for carcinogenic risk associated with RANKL inhibition (Armstrong et al. 2008, Jones et al. 2006, Mori et al. 2007). In *in vivo* rodent cancer models, RANKL inhibition has

	been shown to have a beneficial effect (Branstetter et al. 2009, Canon et al. 2008a, Canon et al. 2008b, Vanderkerken et al. 2003, Yonou et al. 2003, Zhang et al. 2001). If denosumab did affect immune function, a hypothetical association with malignancies linked to immune modulation could exist and would be expected to show the pattern of malignancy associated with immune deficiency.
Evidence source(s) and strength of evidence	This is considered a potential risk based on theoretical concerns and has not been substantiated in the extensive Amgen's clinical study program or in the postmarketing experience (Amgen Prolia EU-RMP v31.0, 2023).
Characterization of the risk	*Frequency* In Amgen's large pivotal PMO study, the subject incidence of new primary malignancy was 4.8% with denosumab and 4.3% with placebo (HR [95% CI] = 1.11 [0.90, 1.37]). In Amgen's pivotal HALT prostate cancer study, the subject incidence of new primary malignancy was 5.1 % with denosumab and 4.6% with placebo (HR [95% Cl] = 1.08 [0.67, 1.72]), and overall survival was 94.1% in each treatment group (HR [95% CI] = 0.99 [0.65, 1.52]). During the placebo-controlled phase of the MOP study, 4 subjects in the denosumab group (3.3%) and no subject in the placebo group reported events of malignancy. The events were prostate cancer in 3 subjects and basal cell carcinoma in 1 subject. Two prostate cancer cases were likely present at baseline based on past medical history. In the 24-month final analysis of the GIOP study, subject incidence of malignancy was 3.0% with denosumab and 1.8% with risedronate (HR [95% CI] = 1.75 [0.69, 4.44]). Subject incidence of serious adverse events of malignancy was 1.8% with denosumab and 1.6% with risedronate. *Severity* Malignancy is a clinically important event requiring medical intervention. *Reversibility* Although some malignancies will respond to treatment, long-term survival will depend upon multiple factors and as such onset of malignancy is rarely considered reversible. *Long-term outcomes* New primary malignancy or progression of existing malignancy may be fatal, life-threatening and long-term outcomes will likely be impacted. *Impact on Quality of Life*

	Malignancy can be life-threatening and generally requires intervention e.g., surgery, radiation, and/or chemotherapy.
Risk group or risk factors	General factors for risk of malignancy include advancing age, diet, cigarette smoking, excessive ethanol consumption, and numerous environmental toxins. In addition, cancer populations are at increased risk for a second primary malignancy because of their existing malignancy, possible genetic predisposition, and exposure to chemotherapy and radiation treatment (Anand et al. 2008, WHO 2011).
Preventability	No preventive measures are known.
Impact on the risk-benefit balance of the product	The potential risk of malignancy has been considered in the product benefit-risk assessment which supports a positive benefit-risk profile in the indicated populations.
Public health impact	Significant public health impact is not anticipated.

SVII.3.2 Presentation of the missing information

There is no missing information for Conexxence (denosumab).

Part II: Module SVIII - Summary of safety concerns

Table 7. Details of important identified and potential risks of Conexxence

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

Part III: Pharmacovigilance Plan

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities will be carried out for the important identified and potential risks described above.

The robust pharmacovigilance system established by Fresenius Kabi enables collection and analysis of safety data from multiple sources including spontaneous notification, literature, regulatory authorities, commercial partners as well as detection and management of signals and risks. When safety information is received, it is triaged and entered into a safety database. Individual case safety reports are reviewed by a safety physician on a case-by-case basis for completeness and accuracy and to assess the seriousness, causal relationship between an adverse event and the drug, as well as the expectedness. If relevant information is missing, Fresenius Kabi will conduct follow-up investigations to collect additional data such as outcome, concomitant medications, concurrent disease(s), etc.

Once Conexxence is marketed, aggregate safety data will be reviewed periodically and compared to the previous period, taking into account the accumulated safety knowledge for the product to identify any safety signals or trends. If a signal is detected, Fresenius Kabi will assess the data in order to validate the signal taking into account previous awareness, strength of the evidence, as well as clinical relevance.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection will include specific adverse reaction follow-up questionnaires to collect relevant safety information in a standardized manner and monitor the frequency and nature of adverse events emerging during clinical trials and post-marketing use of Conexxence related to some of the risks:

Follow-up Questionnaire	Safety concern(s)	Purpose
Hypocalcaemia	Hypocalcaemia	To monitor the nature of hypocalcaemia in patients treated with Conexxence in the postmarketing environment.
Infection	Skin infection leading to hospitalisation Infection	To monitor the nature of skin infections leading to hospitalisation and infections of any type reported in patients treated with Conexxence in the postmarketing environment
Osteonecrosis of the jaw	Osteonecrosis of the Jaw	To monitor the nature of ONJ in patients treated with Conexxence in the postmarketing environment.

Postmarketing reports of potential atypical fracture	Atypical Femoral Fracture	To monitor the nature of AFF in patients treated with Conexxence in the postmarketing environment.
Fracture healing	Fracture healing complications	To monitor the nature of fracture healing complications reported in patients treated with Conexxence in the postmarketing environment.
Malignancy	Malignancy	To monitor the nature of malignancy adverse events reported in patients treated with Conexxence in the postmarketing environment.
Hypersensitivity	Hypersensitivity reactions	To monitor the nature of hypersensitivity reported in patients treated with Conexxence in the postmarketing environment.

For further details on the specific adverse reaction follow-up questionnaires please see Annex 4 of the RMP.

III.2 Additional pharmacovigilance activities

The routine pharmacovigilance activities outlined in Section III.1 Routine pharmacovigilance activities are considered sufficient to further characterize the risks associated with Conexxence. Therefore, no additional pharmacovigilance activities are proposed for the product at this point in time.

III.3 Summary table of additional pharmacovigilance activities

Not applicable.

Part IV: Plans for Post-authorization Efficacy Studies

IV.1 Planned and ongoing post-authorization imposed efficacy studies that are conditions of the marketing authorization or that are specific obligations

There are currently no planned post-authorization efficacy studies for Conexxence.

Part V: Risk Minimization Measures

Risk Minimization Plan

V.1 Routine risk minimization measures

Table 8 Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Important identified risk: **Hypocalcaemia**	**Routine risk communication:** SmPC • Section 4.2, Section 4.3, Section 4.4, Section 4.8. Patient Information leaflet (PIL) • Section 2, Section 4. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Recommendation for correction of hypocalcaemia prior to initiating treatment with Conexxence and clinical monitoring of calcium levels during treatment with Conexxence is included in SmPC Section 4.4. **Other risk minimization measures beyond the Product Information:** Medicine's legal status: prescription only medicine.
Important identified risk: **Skin infection leading to hospitalization**	**Routine risk communication:** SmPC • Section 4.4, Section 4.8. PIL • Section 2, Section 4. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None. **Other risk minimization measures beyond the Product Information:** Medicine's legal status: prescription only medicine.
Important identified risk:	**Routine risk communication:**

Safety concern	Routine risk minimization activities
Osteonecrosis of the jaw	SmPC • Section 4.4, Section 4.8. PIL • Section 2, Section 4. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Recommendations for oral examination, maintenance of good oral hygiene during treatment, management of patients with unavoidable invasive dental procedure, and temporary interruption of treatment if ONJ occurs are included in Section 4.4 of SmPC. **Other risk minimization measures beyond the Product Information:** Medicine's legal status: prescription only medicine.
Important identified risk: **Hypersensitivity reactions**	**Routine risk communication:** SmPC • Section 4.3, Section 4.8. PIL • Section 2, Section 4. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None. **Other risk minimization measures beyond the Product Information:** Medicine's legal status: prescription only medicine.
Important identified risk: **Atypical femoral fracture**	**Routine risk communication**: SmPC • Section 4.4, Section 4.8. PIL • Section 2, Section 4. **Routine risk minimization activities recommending specific clinical measures to address the risk**:

Safety concern	Routine risk minimization activities
	Recommendation for reporting new or unusual thigh, hip, or groin pain is included Section 4.4 of SmPC. **Other risk minimization measures beyond the Product Information**: Medicine's legal status: prescription only medicine.
Important identified risk: **Hypercalcemia in paediatric patients receiving denosumab and after treatment discontinuation**	**Routine risk communication:** SmPC • Section 4.2, Section 4.4, Section 4.8. PIL • Section 2. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None. **Other risk minimization measures beyond the Product Information:** Medicine's legal status: prescription only medicine.
Important potential risk: **Fracture healing complications**	**Routine risk communication:** SmPC • Section 5.3. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None. **Other risk minimization measures beyond the Product Information:** Medicine's legal status: prescription only medicine.
Important potential risk: **Infection**	**Routine risk communication:** SmPC • Section 4.8. PIL • Section 4.

Safety concern	Routine risk minimization activities
	Routine risk minimization activities recommending specific clinical measures to address the risk: None. **Other risk minimization measures beyond the Product Information:** Medicine's legal status: prescription only medicine.
Important potential risk: **Cardiovascular events**	**Routine risk communication:** None. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None. **Other risk minimization measures beyond the Product Information:** Medicine's legal status: prescription only medicine.
Important potential risk: **Malignancy**	**Routine risk communication:** None. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None. **Other risk minimization measures beyond the Product Information:** Medicine's legal status: prescription only medicine.
Missing information **None**	-

V.2 Additional risk minimization measures

Table 9 Additional risk minimization measures by safety concern

Important identified risk **Osteonecrosis of the jaw**	
Additional Risk Minimization Measure	Patient Reminder Card
Objectives	To ensure that patients seek medical attention early, and that health care providers are aware of the need for timely and appropriate measures to diagnose and treat Osteonecrosis of the jaw.
Rationale for the additional risk minimization activity	The purpose of the Patient Reminder Cards is to remind patients about important safety information that they need to be aware of before and during treatment with denosumab (Conexxence) injections for osteoporosis and bone loss, including: • the risk of osteonecrosis of the jaw during treatment with Conexxence; • the need to highlight any problems with their mouth or teeth to their doctors/nurses before starting treatment; • the need to ensure good oral hygiene during treatment; • the need to inform their dentist of treatment with Conexxence and to contact their doctor or dentist if problems with the mouth or teeth occur during treatment.
Target audience and planned distribution path	Patient and Healthcare providers via country specific distribution channels, as agreed with local authorities.
Plans for evaluating the effectiveness of the interventions and criteria for success	Monitor and evaluate postmarketing and clinical study safety data and report in Periodic Safety Update Reports (PSURs). The distribution of the patient reminder card will be tracked to ensure that it was completed to the distribution plan agreed with national agencies. Additional requests for patient reminder cards will also be recorded as an indicator of ongoing use of the patient reminder card. The effectiveness of risk minimization of ONJ in the EU will be monitored periodically through postmarket reporting rates of ONJ.
Evaluation of the effectiveness of risk minimization measure	No change in risk-benefit profile of Conexxence.

V.3 Summary of risk minimization measures

Table 10 Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important identified risk: **Hypocalcaemia**	**Routine risk minimization measures:** • SmPC: Section 4.2, Section 4.3, Section 4.4, Section 4.8 • PIL: Section 2, Section 4 **Other risk minimization measures** • Legal status: prescription only medicine **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Follow-up questionnaire - Hypocalcaemia **Additional pharmacovigilance activities:** • None
Important identified risk: **Skin infection leading to hospitalization**	**Routine risk minimization measures:** • SmPC: Section 4.4, Section 4.8 • PIL: Section 2, Section 4 **Other risk minimization measures** • Legal status: prescription only medicine **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Follow-up questionnaire - Infection **Additional pharmacovigilance activities:** • None
Important identified risk: **Osteonecrosis of the jaw**	**Routine risk minimization measures:** • SmPC: Section 4.4, Section 4.8 • PIL: Section 2, Section 4 **Other risk minimization measures** • Legal status: prescription only medicine **Additional risk minimization measures:** • Patient Reminder Card	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Follow-up questionnaire - Osteonecrosis of the jaw **Additional pharmacovigilance activities:** • None

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important identified risk: **Hypersensitivity reactions**	**Routine risk minimization measures:** • SmPC: Section 4.3, Section 4.8 • PIL: Section 2, Section 4 **Other risk minimization measures** • Legal status: prescription only medicine **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Follow-up questionnaire - Hypersensitivity **Additional pharmacovigilance activities:** • None
Important identified risk: **Atypical femoral fracture**	**Routine risk minimization measures:** • SmPC: Section 4.4, Section 4.8 • PIL: Section 2, Section 4 **Other risk minimization measures** • Legal status: prescription only medicine **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Follow-up questionnaire – AFF **Additional pharmacovigilance activities:** • None
Important identified risk: **Hypercalcemia in paediatric patient receiving denosumab and after treatment discontinuation**	**Routine risk minimization measures:** • SmPC: Section 4.2, Section 4.4, Section 4.8 • PIL: Section 2 **Other risk minimization measures** • Legal status: prescription only medicine **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None
Important potential risk:	**Routine risk minimization measures:** • SmPC: Section 5.3	**Routine pharmacovigilance activities beyond adverse**

Safety concern	Risk minimization measures	Pharmacovigilance activities
Fracture healing complications	**Routine risk minimization activities recommending specific clinical measures to address the risk**: • None **Other risk minimization measures** • Legal status: prescription only medicine **Additional risk minimization measures:** • None	**reactions reporting and signal detection:** • Follow-up questionnaire – Fracture healing complications **Additional pharmacovigilance activities:** • None
Important potential risk: **Infection**	**Routine risk minimization measures:** • SmPC: Section 4.8 • PIL: Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk**: • None **Other risk minimization measures** • Legal status: prescription only medicine **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Follow-up questionnaire – Infection **Additional pharmacovigilance activities:** • None
Important potential risk: **Cardiovascular events**	**Routine risk minimization measures:** • None **Other risk minimization measures** • Legal status: prescription only medicine **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important potential risk: **Malignancy**	**Routine risk minimization measures:** • None **Other risk minimization measures** • Legal status: prescription only medicine **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Follow-up questionnaire – Malignancy **Additional pharmacovigilance activities:** • None
Missing information **None**	-	-

Part VI: Summary of the Risk Management Plan for Conexxence (denosumab 60 mg)

This is a summary of the Risk Management Plan for Conexxence. The RMP details important risks of Conexxence, how these risks can be minimized, and how more information will be obtained about Conexxence risks and uncertainties (missing information).

The Conexxence's SmPC and PIL give essential information to healthcare professionals and patients, respectively on how denosumab should be used.

This summary of the RMP for Conexxence 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 Conexxence RMP.

I. The medicine and what it is used for

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

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

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

Important risks of Conexxence, together with measures to minimize such risks, are outlined below.

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

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

Together, these measures constitute routine risk minimization measures.

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

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

II.A List of important risks and missing information

Important risks of Conexxence are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Conexxence. 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	• Hypocalcaemia • Skin infection leading to hospitalization • Osteonecrosis of the jaw • Hypersensitivity reactions • Atypical femoral fracture • Hypercalcemia in paediatric patients receiving denosumab and after treatment discontinuation
Important potential risks	• Fracture healing complications • Infection • Cardiovascular events • Malignancy
Missing information	• None

II.B Summary of important risks

Important identified risk: Hypocalcaemia	
Evidence for linking the risk to the medicine	The source of information is clinical/safety and postmarketing data of the reference product Amgen Prolia (EU-RMP v31.0, 2023) and medical literature.
Risk factors and risk groups	Risk factors include severe renal impairment and hyperphosphatemia. Other risks factors may include a history of hypoparathyroidism, parathyroid hormone resistance, vitamin D deficiency or resistance, thyroid surgery, parathyroid surgery, malabsorption syndromes, excision of small intestine, severe renal impairment (creatinine clearance <30 mL/min), dialysis, and some medications (Finkelstein 2001).
Risk minimization measures	**Routine risk communication:** SmPC: Section 4.2, Section 4.3, Section 4.4, Section 4.8 PIL: Section 2, Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** Recommendation for correction of hypocalcaemia prior to initiating treatment with Conexxence and clinical monitoring of calcium levels during treatment with Conexxence is included in SmPC Section 4.4. **Other risk minimization measures beyond the Product Information:** Medicine's legal status: prescription only medicine. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	None
Important identified risk: Skin infection leading to hospitalization	
Evidence for linking the risk to the medicine	The source of information is clinical/safety data of the reference product Amgen Prolia (EU-RMP v31.0, 2023) and medical literature.
Risk factors and risk groups	Risk factors for infection in general include increasing age, immunosuppression associated with cancer, diabetes, HIV/ AIDS, immunosuppressant drugs (e.g., corticosteroids, arthritis medications, and chemotherapy drugs), substance abuse, and malnutrition. Risk factors for

	skin infection in older patients include skin wounds, peripheral vascular disease, eczema/dermatitis, and venous stasis disorders.
Risk minimization measures	**Routine risk communication:** SmPC: Section 4.4, Section 4.8. PIL: Section 2, Section 4. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** Medicine's legal status: prescription only medicine. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	None
Important identified risk: Osteonecrosis of the jaw	
Evidence for linking the risk to the medicine	The source of information is clinical/safety data of the reference product Amgen Prolia (EU-RMP v31.0, 2023) and medical literature.
Risk factors and risk groups	Risk factors include duration of exposure to denosumab, prior bisphosphonate use (particularly for extended periods of time), older age, periodontal disease, dentoalveolar surgery, trauma from poorly fitting dentures, malignancy, chemotherapy, corticosteroids, smoking, systemic or regional infection, immune-compromised state predisposing to increased risk of infection, hypercoagulable state secondary to underlying malignancy, and vascular insufficiency due to thrombosis (Mehrotra and Ruggiero 2006, Ruggiero et al. 2006).
Risk minimization measures	**Routine risk communication:** SmPC: Section 4.4, Section 4.8 PIL: Section 2, Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** Recommendations for oral examination, maintenance of good oral hygiene during treatment, management of patients with unavoidable invasive

	dental procedure, and temporary interruption of treatment if ONJ occurs are included in Section 4.4 of SmPC. **Other risk minimization measures beyond the Product Information:** Medicine's legal status: prescription only medicine. **Additional risk minimization measures:** Patient Reminder Card
Additional pharmacovigilance activities	None
Important identified risk: Hypersensitivity reactions	
Evidence for linking the risk to the medicine	The source of information is postmarketing data of the reference product Amgen Prolia (EU-RMP v31.0, 2023).
Risk factors and risk groups	Known hypersensitivity to denosumab and any of its excipients.
Risk minimization measures	**Routine risk communication:** SmPC: Section 4.3, Section 4.8. PIL: Section 2, Section 4. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None. **Other risk minimization measures beyond the Product Information:** Medicine's legal status: prescription only medicine. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	None
Important identified risk: Atypical femoral fracture	
Evidence for linking the risk to the medicine	The source of information is clinical/safety data of the reference product Amgen Prolia (EU-RMP v31.0, 2023) and medical literature.

Risk factors and risk groups	Long-term antiresorptive treatment has been associated with AFF. Corticosteroids have also been reported in the literature to potentially be associated with AFF (Giusti et al. 2011, Meier et al. 2012). Atypical femoral fractures have also been reported in patients with certain comorbid conditions (e.g., vitamin D deficiency, RA, hypophosphatasia) and with use of bisphosphonates, glucocorticoids, and proton pump inhibitors (Shane et al. 2010).
Risk minimization measures	**Routine risk communication**: SmPC: Section 4.4, Section 4.8. PIL: Section 2, Section 4. **Routine risk minimization activities recommending specific clinical measures to address the risk**: Recommendation for reporting new or unusual thigh, hip, or groin pain is included Section 4.4 of SmPC. **Other risk minimization measures beyond the Product Information**: Medicine's legal status: prescription only medicine. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	None
Important identified risk: Hypercalcemia in paediatric patients receiving denosumab and after treatment discontinuation	
Evidence for linking the risk to the medicine	The source of information is clinical/safety and postmarketing data of the reference product Amgen Prolia (EU-RMP v31.0, 2023).
Risk factors and risk groups	Paediatric patients with growing skeletons and high bone turnover disease states (such as OI).
Risk minimization measures	**Routine risk communication:** SmPC: Section 4.2, Section 4.4, Section 4.8. PIL: Section 2. **Routine risk minimization activities recommending specific clinical measures to address the risk:**

	None. **Other risk minimization measures beyond the Product Information:** Medicine's legal status: prescription only medicine. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	None
Important potential risk: Fracture healing complications	
Evidence for linking the risk to the medicine	This is a theoretical risk based on the mechanism of action (Amgen Prolia EU-RMP v31.0, 2023).
Risk factors and risk groups	General risk factors for fracture healing complications are thought to include older age, diabetes, use of medications such as non-steroidal anti-inflammatory drugs and corticosteroids, smoking, excessive alcohol use, and poor nutrition (Gaston and Simpson 2007, Hernandez et al. 2012).
Risk minimization measures	**Routine risk communication:** SmPC: Section 5.3. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None. **Other risk minimization measures beyond the Product Information:** Medicine's legal status: prescription only medicine. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	None
Important potential risk: Infection	
Evidence for linking the risk to the medicine	This is considered a potential risk based on theoretical concerns which has not been substantiated in the Amgen's extensive clinical study program or in the postmarketing experience (Amgen Prolia EU-RMP v31.0, 2023).

Risk factors and risk groups	Risk factors for infection in general include increasing age, immunosuppression associated with cancer, diabetes, HIV/AIDS, immunosuppressant drugs (e.g., corticosteroids, arthritis medications, and chemotherapy drugs), substance abuse, and malnutrition.
Risk minimization measures	**Routine risk communication:** SmPC: Section 4.8. PIL: Section 4. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None. **Other risk minimization measures beyond the Product Information:** Medicine's legal status: prescription only medicine. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	None
Important potential risk: Cardiovascular events	
Evidence for linking the risk to the medicine	This is a theoretical risk based on epidemiological data demonstrating elevated OPG in patients with cardiovascular disease (Amgen Prolia EU-RMP v31.0, 2023).
Risk factors and risk groups	The denosumab development program comprises studies of older subject populations (e.g., osteoporosis, cancer) that are likely to have a higher incidence of pre-existing cardiovascular conditions and, thus, a higher incidence of cardiovascular toxicities than that of the general population (Hak et al. 2000, Schulz et al. 2004)
Risk minimization measures	**Routine risk communication:** None **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** Medicine's legal status: prescription only medicine. **Additional risk minimization measures:**

	None
Additional pharmacovigilance activities	None
Important potential risk: Malignancy	
Evidence for linking the risk to the medicine	This is considered a potential risk based on theoretical concerns and has not been substantiated in the extensive Amgen's clinical study program or in the postmarketing experience (Amgen Prolia EU-RMP v31.0, 2023).
Risk factors and risk groups	General factors for risk of malignancy include advancing age, diet, cigarette smoking, excessive ethanol consumption, and numerous environmental toxins. In addition, cancer populations are at increased risk for a second primary malignancy because of their existing malignancy, possible genetic predisposition, and exposure to chemotherapy and radiation treatment (Anand et al. 2008, WHO 2011).
Risk minimization measures	**Routine risk communication:** None **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** Medicine's legal status: prescription only medicine. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	None
Missing information: None	

II.C Post-authorization development plan

II.C.1 Studies that are conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Conexxence.

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

There are no studies planned.

Annex 4 – Specific adverse drug reaction follow-up forms.

Follow-up Form Title	Version number
Hypocalcemia	1.0
Infection	1.0
Osteonecrosis of the Jaw	1.0
Postmarketing reports of potential atypical fracture	1.0
Fracture healing	1.0
Malignancy	1.0
Hypersensitivity	1.0

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AER# | Safety database number

Patient identifier | Study number

Above information to be filled by Fresenius Kabi.

DENOSUMAB Core Questionnaire: **Hypocalcemia**

This form is subject to applicable laws governing the protection of personal information. The information provided on this form may be transferred and processed outside of the country in which it is collected. Fresenius Kabi does not wish to receive information through which a patient can be identified therefore please do not provide any information other than the specific information required by this form. This prohibition includes, for example, name, address, telephone number and government issued identifier.

Patient information (Please indicate dates as DD/MM/YYYY)

Patient initials | Gender: ☐ Female ☐ Male | Date of event onset | Date of this report

Weight: ☐ lb ☐ kg

Event reported term

Age at time of event:

DENOSUMAB treatment information (please indicate dates as DD/MM/YYYY)

DENOSUMAB indication

☐ Postmenopausal osteoporosis

☐ Bone loss from hormone ablation therapy
Please specify diagnosis

☐ Advanced cancer with bone metastasis
Please specify cancer

☐ Other (please specify)

☐ Don't know

DENOSUMAB dosage

☐ 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
☐ Yes ☐ No ☐ Unknown

If yes, please specify

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

If yes, date of first dose following start of event

1 of 4 Version 1.0

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AER#

Safety database number

Patient identifier

Study number

Above information to be filled by Fresenius Kabi.

DENOSUMAB Core Questionnaire: **Hypocalcemia**

Signs and symptoms (check all that apply)

- ☐ Numbness (Specify if involving digits and/or peri-oral region)
- ☐ Muscle cramping
- ☐ Paresthesia
- ☐ Syncope
- ☐ Tetany
- ☐ Convulsions
- ☐ Muscle twitching
- ☐ None
- ☐ Other

Diagnosis (check all that apply)

Serum calcium at time of event: ☐ mg/dL ☐ Unknown

Please provide serum albumin result:

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

If yes, what were the ionized calcium levels?
☐ mg/dL

Serum creatinine at time of event was > 2.0 X times upper limit of normal? (please provide result)
☐ Yes ☐ No ☐ Unknown

Hypocalcemia-induced EKG Changes (QT prolongation)? ☐ Yes ☐ No ☐ Unknown

Treatment of adverse reaction or hypocalcaemia (check all that apply)

Treated only as an outpatient? ☐ Yes ☐ No

If yes, route of calcium replacement:
☐ IV ☐ Oral ☐ Unknown

Treated in the ER? ☐ Yes ☐ No

If yes, route of calcium replacement:
☐ IV ☐ Oral ☐ Unknown

Treatment included general hospital admission for calcium replacement
☐ Yes ☐ No

If yes, route of calcium replacement:
☐ IV ☐ Oral ☐ Unknown

Treatment included ICU admission?
☐ Yes ☐ No

If yes, route of calcium replacement:
☐ IV ☐ Oral ☐ Unknown

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

Anti-arrhythmic medications?
☐ Yes ☐ No ☐ Unknown

If yes, please provide the details such as names and dates of treatment Anti-arrhythmic medications

Other treatment?
☐ Yes ☐ No ☐ Unknown

If yes, please specify

FRESENIUS KABI
caring for life

AER# | Safety database number

Patient identifier | Study number

Above information to be filled by Fresenius Kabi.

DENOSUMAB Core Questionnaire: **Hypocalcemia**

Risk factors (check all that apply)

Medical history

Does the patient have any of the following risk factors:

- ☐ Acute pancreatitis
- ☐ History of parathyroid disease
- ☐ History of malignancy (please specify)
- ☐ Hyperphosphatemia
- ☐ Recent surgery (please specify)
- ☐ History of chronic renal disease
- ☐ History of hypoalbuminemia
- ☐ Hypoproteinemia
- ☐ Magnesium deficiency
- ☐ Sepsis

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

☐ Prior hypocalcemia event (before denosumab treatment)
Please provide the dates and details of prior hypocalcemia event

Treatment medication

Antineoplastic agents? (Check which apply)
- ☐ cisplatin
- ☐ cytosine arabinoside
- ☐ Other
- ☐ None

Antimicrobials? (Check which apply)
- ☐ pentamidine
- ☐ ketoconazole
- ☐ Other
- ☐ None

FRESENIUS KABI
caring for life

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DENOSUMAB Core Questionnaire: **Hypocalcemia**

Concomitant medications

Taking vitamin D supplement? ☐ Yes ☐ No ☐ Unknown

If yes, please provide dose and dates:

Taking calcium supplement? ☐ Yes ☐ No ☐ Unknown

If yes, please provide dose and dates:

Other concomitant medications **(please provide drug name, dose and dates)**

Hypocalcemic Event Resolved ☐ Yes ☐ No ☐ Unknown

If yes, what date? **(DD/MM/YYYY)**

Reporter Name:

Address:

City: State/ province:

Country: Postal code:

Email:

Phone **(Include country code)**:

Signature:

Title: Date:

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FRESENIUS KABI
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DENOSUMAB Core Questionnaire: **Infection**

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Patient information (Please indicate dates as DD/MM/YYYY)

Patient initials | Gender: ☐ Female ☐ Male | Date of event onset | Date of this report

Weight: ☐ lb ☐ kg

Age at time of event:

Event reported term

DENOSUMAB treatment information (Please indicate dates as DD/MM/YYYY)

DENOSUMAB indication

☐ Postmenopausal osteoporosis

☐ Bone loss from hormone ablation therapy
Please specify diagnosis

☐ Advanced cancer with bone metastasis
Please specify cancer

☐ Other (Please specify)

☐ Don't know

DENOSUMAB dosage

☐ 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
☐ Yes ☐ No ☐ Unknown

If yes, please specify

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

If yes, date of first dose following start of event

1 of 9 Version 1.0

FRESENIUS KABI
caring for life

AER# | Safety database number

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DENOSUMAB Core Questionnaire: **Infection**

Signs and symptoms (Check all that apply, provide dates of onset, resolution if available)

- ☐ Chills
- ☐ Cough
- ☐ Diarrhea
- ☐ Discharge location/description
- ☐ Fever
- ☐ Night sweats
- ☐ Pain (provide location)
- ☐ Prolonged fatigue
- ☐ Rash (provide location)
- ☐ Shortness of breath
- ☐ Swelling (provide location)
- ☐ Organ system affected:
  - ☐ Cardiac
  - ☐ Ear/nose
  - ☐ Gastrointestinal
  - ☐ Kidney/genito-urinary
  - ☐ Musculoskeletal (including joints)
  - ☐ Other
  - ☐ Nervous (cerebrospinal fluid)
  - ☐ Respiratory
  - ☐ Skin Location
  - ☐ Systemic (bacteremia and/or sepsis)
  - ☐ Throat

Evaluations, diagnosis and laboratory measures (Please attach copy of report)

Diagnosis	Results/Units	Reference Range/Units	Date	Report attached Y	Report attached N

FRESENIUS KABI
caring for life

AER#	Safety database number
Patient identifier	**Study number**

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DENOSUMAB Core Questionnaire: **Infection**

Evaluations, diagnosis and laboratory measures (please attach copy of report)

Diagnosis	Results/Units	Reference Range/Units	Date	Report attached	
				Y	N

FRESENIUS KABI
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DENOSUMAB Core Questionnaire: **Infection**

Reports/Relevant findings (please provide dates as DD/MM/YYYY, baseline information and indicate attachments, if available)

Check which infection applies

- ☐ Cardiac Infections
  - ☐ Endocarditis
  - ☐ Pericarditis (purulent; tuberculous)
  - ☐ Other (please specify)
- ☐ Ear and labyrinth infections
  - ☐ Otitis media
  - ☐ Otitis externa
  - ☐ Other (please specify)
- ☐ Gastrointestinal/abdominal infections
  - ☐ Colitis
  - ☐ Diverticulitis
  - ☐ Appendicitis
  - ☐ Abdominal sepsis (including peritonitis)
  - ☐ Hepatic abscess
  - ☐ Hepatitis B
  - ☐ Hepatitis C
  - ☐ Other (please specify)
- ☐ Wound and skin infections
  - ☐ Cellulitis
  - ☐ Erysipelas
  - ☐ Necrotizing fasciitis
  - ☐ Abscess
  - ☐ Other skin infections (please specify)
- ☐ Musculoskeletal and connective tissue infections
  - ☐ Osteomyelitis
  - ☐ Septic arthritis
  - ☐ Other (please specify)
- ☐ Nervous system infections
  - ☐ Meningitis
  - ☐ Encephalitis
  - ☐ Other (please specify)

Evaluations, diagnosis and laboratory measures (please attach copy of report)

Check which infection applies

- ☐ Respiratory tract infections
  - ☐ Pneumonia
  - ☐ Pulmonary TB
  - ☐ Lung abscess
  - ☐ Legionella pneumonia
  - ☐ Mycoplasma pneumonia
  - ☐ Other (please specify)

FRESENIUS KABI
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DENOSUMAB Core Questionnaire: **Infection**

- ☐ Kidney and genito-urinary tract infections
  - ☐ Cystitis
  - ☐ Pyelonephritis
  - ☐ Urinary tract infection
  - ☐ Other (please specify)
- ☐ Systemic infections
  - ☐ Bacteremia
  - ☐ Sepsis
  - ☐ Toxic shock syndrome
  - ☐ Other (please specify)
- ☐ Other infections (please specify)
- ☐ Parasitic evaluation (ova, etc.)
- ☐ Opportunistic infections
  - ☐ Aspergillus (invasive forms only)
  - ☐ Blastomycosis pulmonary or extra-pulmonary infections
  - ☐ Candidiasis systemic
  - ☐ Coccidioidemycosis secondary/systemic
  - ☐ Cryptococcal infection - pulmonary and non-pulmonary
  - ☐ Cytomegalovirus - include systemic site
  - ☐ Herpes simplex (meningitis or encephalitis)
  - ☐ Herpes zoster (only systemic or disseminated: involving 2 or more dermatomes)
  - ☐ Histoplasma infections - chronic disseminated or sever acute
  - ☐ Mucormycosis (=zygomycosis) including infections due to Rhizopus, Mucor and Absidia of lung, genito-urinary tract, kidney, GIT, skin
  - ☐ Mycobacterium tuberculosis
  - ☐ Non-tuberculosis mycobacterium
  - ☐ Nocardia inection - of brain, lungs, kidney, skin
  - ☐ Paracoccidioides infections of lungs, skin other
  - ☐ Pneumocystis carinii pneumonia
  - ☐ Sporotrichosis - disseminated infections
  - ☐ Toxoplasmosis encephalitis or disseminated
  - ☐ Other opportunistic infections (please specify)

FRESENIUS KABI
caring for life

AER# | Safety database number

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DENOSUMAB Core Questionnaire: **Infection**

Reports/Relevant findings (continued)

(please provide dates, baseline information and indicate attachments if available)

Diagnostics

Cultures done ☐ Yes ☐ No ☐ Unknown

If yes, check which apply:

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

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

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

☐ Cerebrospinal fluid culture
- Culture positive ☐ Yes ☐ No ☐ Unknown
- If yes, which: ☐ Viral ☐ Fungal ☐ Bacterial
- Pathogen identified:

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

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

☐ Catheter Tip/Line
- Culture positive ☐ Yes ☐ No ☐ Unknown
- If yes, which: ☐ Viral ☐ Fungal ☐ Bacterial
- Pathogen identified:

FRESENIUS KABI
caring for life

AER# | Safety database number

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DENOSUMAB Core Questionnaire: **Infection**

- ☐ PPD placement
  - If yes, PPD positive ☐ Yes ☐ No ☐ Unknown
- ☐ Parasitic evaluation (ova, etc.)
- ☐ X-ray ☐ Yes ☐ No ☐ Unknown
- ☐ MRI ☐ Yes ☐ No ☐ Unknown
- ☐ CT scan ☐ Yes ☐ No ☐ Unknown
- ☐ Bone scan ☐ Yes ☐ No ☐ Unknown
- ☐ Other
- ☐ Rapid test
- ☐ Serum titres
- ☐ Hospital discharge report
- ☐ Other consult report
- ☐ Provide final diagnosis and treatment, if available (please specify)
- ☐ Outcome and resolution date

Treatment of adverse reaction of infection

- ☐ ER antibiotics ☐ Yes ☐ No ☐ Unknown
  - If yes, route: ☐ IV ☐ Oral ☐ SC ☐ Both; oral and IV
- ☐ In-hospital antibiotics ☐ Yes ☐ No ☐ Unknown
  - If yes, route: ☐ IV ☐ Oral ☐ Both; oral and IV
- ☐ Required hospital admission ☐ Yes ☐ No ☐ Unknown
- ☐ ICU admission ☐ Yes ☐ No ☐ Unknown
  - If yes, reason for admission:
- Overall length of hospital stay:
  - ☐ ≤ 1 day ☐ > 1 day ☐ ≤ 7 days ☐ > 7 days
- ☐ Other in-hospital treatment
  - ▸ Antivirals ☐ Yes ☐ No ☐ Unknown
    - If yes, route: ☐ IV ☐ Oral
  - ▸ Antifungals ☐ Yes ☐ No ☐ Unknown
    - If yes, route: ☐ IV ☐ Oral
  - ▸ Surgery ☐ Yes ☐ No ☐ Unknown
  - ▸ Hyperbaric Oxygen ☐ Yes ☐ No ☐ Unknown

7 of 9

Version 1.0

FRESENIUS KABI
caring for life

AER#

Safety database number

Patient identifier

Study number

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DENOSUMAB Core Questionnaire: **Infection**

Patient medical history (Please provide history, dates, severity of reaction and intervention)

Please specify any post operative complications, chronic disease or infection, etc.

- ☐ Chronic lung disease
- ☐ Hepatitis
- ☐ Chronic kidney disease
- ☐ Liver disease
- ☐ Congenital infections/malformations
- ☐ Osteomyelitis
- ☐ HIV
- ☐ Diabetes mellitus
- ☐ Cancer (specify)
- ☐ Recent wounds/infections
- ☐ Immunosuppression
- ☐ Known exposure to TND inhibitors
- ☐ Chemotherapy
- ☐ Malnutrition/failure to thrive
- ☐ Exposure to infectious agents
  - ☐ Personal contact
  - ☐ Body fluids
  - ☐ Share personal items (razor, needles, etc.)
  - ☐ Potentially contaminated food/liquid
  - ☐ Hospital acquired
  - ☐ Other
- ☐ Steroid exposure
- ☐ Insect/tick bite
- ☐ Drug or IV drug abuse:
  - ▸ Type
  - ▸ Amount
  - ▸ Frequency
- ☐ Alcohol/tobacco abuse:
  - ▸ Type
  - ▸ Amount
  - ▸ Frequency
- ☐ Indwelling catheters
- ☐ Recent skin injury
- ☐ Recent travel (specify)
- ☐ Exposure to animals/zoonotic diseases (exposure to infected animal)
- ☐ Unprotected sex
- ☐ Immobility
- ☐ Nursing home resident
- ☐ Occupational exposure
- ☐ Ostomy
- ☐ Post influenza
- ☐ Surgery < 30 days
- ☐ TB exposure
- ☐ Other history/risk factors

8 of 9

Version 1.0

FRESENIUS KABI
caring for life

AER#

Safety database number

Patient identifier

Study number

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DENOSUMAB Core Questionnaire: **Infection**

Reporter Name:

Address:

City: State/ province:

Country: Postal code:

Email:

Phone (Include country code):

Signature:

Title: Date:

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FRESENIUS KABI
caring for life

AER# | Safety database number

Patient identifier | Study number

Above information to be filled by Fresenius Kabi.

DENOSUMAB Core Questionnaire: **Osteonecrosis of the Jaw**

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Patient information (please indicate dates as DD/MM/YYYY)

Patient initials | Gender: ☐ Female ☐ Male | Date of event onset | Date of this report

Weight: ☐ lb ☐ kg

Age at time of event:

Event reported term

DENOSUMAB treatment information (please indicate dates as DD/MM/YYYY)

DENOSUMAB indication

☐ Postmenopausal osteoporosis

☐ Bone loss from hormone ablation therapy
Please specify diagnosis

☐ Advanced cancer with bone metastasis
Please specify cancer

☐ Other (Please specify)

☐ Don't know

DENOSUMAB dosage

☐ 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
☐ Yes ☐ No ☐ Unknown

If yes, please specify

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

If yes, date of first dose following start of event

1 of 7 Version 1.0

FRESENIUS KABI
caring for life

AER#

Safety database number

Patient identifier

Study number

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DENOSUMAB Core Questionnaire: **Osteonecrosis of the Jaw**

Evidence of exposed bone (please indicate dates as DD/MM/YYYY)

Visible evidence of exposed bone, or bone that can be probed through an intraoral or extraoral fistula(e) in the maxillofacial region: ☐ Yes ☐ No ☐ Unknown

If yes, please describe

Date exposed bone was first visualized / probed:

Exposed bone or probed bone that has persistent for more than eight weeks: ☐ Yes ☐ No ☐ Unknown

If yes, please describe

Prior history of radiation therapy to jaw: ☐ Yes ☐ No ☐ Unknown

If yes, please describe

Prior history of metastatic disease to jaw: ☐ Yes ☐ No ☐ Unknown

If yes, please describe

Prior history of metastatic disease to jaw

Please indicate the location of involved area(s) on the diagram (mark site(s) clearly with an 'X')

- ☐ Right maxilla, teeth and lateral jaw
- ☐ Left maxilla, teeth and lateral jaw
- ☐ Right maxilla, medial jaw
- ☐ Left maxilla, medial jaw
- ☐ Right mandible teeth and lateral jaw
- ☐ Left mandible teeth and lateral jaw
- ☐ Right mandible, medial jaw
- ☐ Left mandible, medial jaw
- ☐ Maxilla hard palate
- ☐ Other (please specify)

2 of 7

Version 1.0

FRESENIUS KABI
caring for life

AER#

Safety database number

Patient identifier

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DENOSUMAB Core Questionnaire: **Osteonecrosis of the Jaw**

Oral findings

Evidence of infecton:

☐ Yes ☐ No ☐ Unknown

If yes, please describe

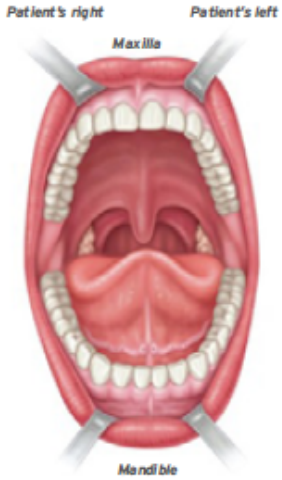
Exposed bone at the site of extraction:

☐ Yes ☐ No ☐ Unknown

Complete coverage of involved area(s) by mucosa:

☐ Yes ☐ No ☐ Unknown

If yes, please describe



Clinical symptoms

(Please indicate dates as DD/MM/YYYY)

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

Please describe the clinical signs/symptoms/location:

Consultations (please indicate dates as DD/MM/YYYY)

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

If yes, please give date of examination

Please provide any consult reports, radiographs, pictures if available

FRESENIUS KABI
caring for life

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DENOSUMAB Core Questionnaire: **Osteonecrosis of the Jaw**

Treatment for adverse reaction of osteonecrosis of the jaw

(Please indicate what treatments were admisistered and indicate dates as DD/MM/YYYY)

Antibiotics ☐ Yes ☐ No ☐ Unknown

If yes, agent(s)/route/dose

Start date Stop date

Please descibe outcomes of treatment

Oral rinses ☐ Yes ☐ No ☐ Unknown

If yes, agent(s)/dose

Please descibe outcomes of treatment

Oral surgery ☐ Yes ☐ No ☐ Unknown

If yes, type of surgery

Start date Stop date

Please descibe outcomes of treatment

Hospitalization ☐ Yes ☐ No ☐ Unknown

If yes, reason for hospitalization

Start date Stop date

Please descibe outcomes of treatment

FRESENIUS KABI
caring for life

AER# | Safety database number

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DENOSUMAB Core Questionnaire: **Osteonecrosis of the Jaw**

Dental history (please indicate dates as DD/MM/YYYY)

History or poor oral hygiene ☐ Yes ☐ No ☐ Unknown

Dental extraction recently ☐ Yes ☐ No ☐ Unknown — If yes, date of procedure

Dental surgery recently ☐ Yes ☐ No ☐ Unknown — If yes, date of procedure

Periodontal disease including gingival bleeding, clculus, etc. ☐ Yes ☐ No ☐ Unknown — Start date — End date

Draining fistula in affected area ☐ Yes ☐ No ☐ Unknown — Start date — End date

Dental abscess in affected area ☐ Yes ☐ No ☐ Unknown — Start date — End date

Osteomyelitis in affected area ☐ Yes ☐ No ☐ Unknown — Start date — End date

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

History of dentures/ dental appliance/ implant ☐ Yes ☐ No ☐ Unknown — Please specify ☐ Upper ☐ Lower

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

FRESENIUS KABI
caring for life

AER# | Safety database number

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DENOSUMAB Core Questionnaire: **Osteonecrosis of the Jaw**

Medications (please indicate dates as DD/MM/YYYY)

PO bisphosphonate ☐ Yes ☐ No ☐ Unknown

If yes, agent(s)/dose

Start date | Stop date

IV bisphosphonate ☐ Yes ☐ No ☐ Unknown

If yes, agent(s)/dose

Start date | Stop date

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

If yes, agent(s)/dose

Start date | Stop date

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

If yes, agent(s)/dose

Start date | Stop date

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

If yes, agent(s)/dose

Start date | Stop date

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

If yes, agent(s)/dose

Start date | Stop date

6 of 7

Version 1.0

FRESENIUS KABI
caring for life

AER#

Safety database number

Patient identifier

Study number

Above information to be filled by Fresenius Kabi.

DENOSUMAB Core Questionnaire: **Osteonecrosis of the Jaw**

Other history (please indicate dates as DD/MM/YYYY)

Current smoker ☐ Yes ☐ No ☐ Unknown

If yes, estimated number of pack-years

If past smoker, stop date

Alcohol consumption ☐ Yes ☐ No ☐ Unknown

If yes, estimated drinks per week

Diabetes ☐ Yes ☐ No ☐ Unknown

If yes, which type ☐ Type 1 ☐ Type 2

Patient reminder card status (for EU Patients)

Received a patient reminder card prior to the ONJ event: ☐ Yes ☐ No ☐ Unknown

Reporter Name:

Address:

City: State/ province:

Country: Postal code:

Email:

Phone (Include country code):

Signature:

Title: Date:

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DENOSUMAB Core Questionnaire: **Postmarketing reports of potential atypical fracture (low energy, subtrochanteric/ femoral shaft fractures)**

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Patient information (Please indicate dates as DD/MM/YYYY)

Patient initials

Gender: ☐ Female ☐ Male

Weight: ☐ lb ☐ kg

Date of event onset

Date of this report

Age at time of event:

Event reported term

DENOSUMAB treatment information (please indicate dates as DD/MM/YYYY)

DENOSUMAB indication

☐ Postmenopausal osteoporosis

☐ Bone loss from hormone ablation therapy
Please specify diagnosis

☐ Advanced cancer with bone metastasis
Please specify cancer

☐ Other (please specify)

☐ Don't know

DENOSUMAB dosage

☐ 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

☐ Yes ☐ No ☐ Unknown

If yes, please specify

Doses of denosumab given after event began

☐ Yes ☐ No ☐ Unknown

If yes, date of first dose following start of event

FRESENIUS KABI
caring for life

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Patient identifier

Study number

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DENOSUMAB Core Questionnaire: **Postmarketing reports of potential atypical fracture (low energy, subtrochanteric/ femoral shaft fractures)**

Diagnosis (Check all that apply)

Location of fracture

- ☐ Femur neck
- ☐ Femur distal
- ☐ Femur midshaft
- ☐ Femur intertrochanter
- ☐ Femur subtrochanter
- ☐ Other location (Please specify)

Diagnostic imaging used to confirm fracture:
☐ X-ray ☐ CT scan ☐ MRI

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

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

Was this a pathological fracture associated with bone tumor or miscellaneous bone diseases (e.g. Pagat's disease, fibrous dysplasia)?
☐ Yes ☐ No ☐ Unknown

Type of fracture

- ☐ Transverse
- ☐ Spiral
- ☐ Oblique
- ☐ Not reported

Fracture radiology report includes

Simple transverse or oblique (30°) fracture with beaking of the cortex:
☐ Yes ☐ No ☐ Not reported

Diffuse cortical thickening of the proximal femoral shaft:
☐ Yes ☐ No ☐ Not reported

Type of trauma reported at time of fracture

- ☐ No trauma
- ☐ Fall from standing height or less
- ☐ Fall on stairs, steps or curbs
- ☐ Fall from 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

FRESENIUS KABI
caring for life

AER# | Safety database number

Patient identifier | Study number

Above information to be filled by Fresenius Kabi.

DENOSUMAB Core Questionnaire: **Postmarketing reports of potential atypical fracture (low energy, subtrochanteric/ femoral shaft fractures)**

Early symptom of pain over fracture site

- ☐ Pain at site at rest
- ☐ Pain at site with weight bearing
- ☐ None

Fracture healed (union) within 6 months

☐ Yes ☐ No ☐ Unknown

If yes,

Date of fracture union (DD/MM/YYYY)

Patient able to walk without assistance

☐ Yes ☐ No ☐ Unknown

Fracture union confirmed through imaging

☐ Yes ☐ No ☐ Unknown

If yes, check all diagnostic imaging that applies

☐ X-ray ☐ CT scan ☐ MRI

Treatment of adverse reaction of potential atypical fracture

(please provide dates and indicate attachments if available)

Methods to reduce and set fracture

- ☐ Non-surgical reduction
- ☐ Casting
- ☐ Surgery
- ☐ Revision surgery (2nd surgery)
- ☐ Other
- ☐ Unknown

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DENOSUMAB Core Questionnaire: **Postmarketing reports of potential atypical fracture (low energy, subtrochanteric/ femoral shaft fractures)**

Medical history/risk factors (please 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 metastases
☐ Yes ☐ No ☐ Unknown

If yes, did metastasis involve bone?
☐ Yes ☐ No ☐ Unknown

Metastasis in femur where fracture occured?
☐ Yes ☐ No ☐ Unknown

Prior Osteoporosis therapy

- ☐ Estrogen
- ☐ Selective estrogen receptor modular (SERM)
- ☐ Bisphophonate (please indicate)
  - ☐ Intravenous
  - ☐ Oral

If checked, how long has therapy been received?

- ☐ Parathyroid hormone

Past medical and surgical history:

4 of 5

Version 1.0

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DENOSUMAB Core 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:

Country: Postal code:

Email:

Phone (include country code):

Signature:

Title: Date:

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DENOSUMAB Core Questionnaire: **Fracture healing**

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Patient information (Please indicate dates as DD/MM/YYYY)

Patient initials

Gender: ☐ Female ☐ Male

Weight: ☐ lb ☐ kg

Date of event onset

Date of this report

Event reported term

Age at time of event:

DENOSUMAB administrative information (Please indicate dates as DD/MM/YYYY)

DENOSUMAB indication

☐ Postmenopausal osteoporosis

☐ Bone loss from hormone ablation therapy
Please specify diagnosis

☐ Advanced cancer with bone metastasis
Please specify cancer

☐ Other (Please specify)

☐ Don't know

DENOSUMAB dosage

☐ 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

☐ Yes ☐ No ☐ Unknown

If yes, please specify

Doses of denosumab given after event began

☐ Yes ☐ No ☐ Unknown

If yes, date of first dose following start of event

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AER# | Safety database number

Patient identifier | Study number

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DENOSUMAB Core Questionnaire: **Fracture healing**

Diagnosis (Check all that apply, please indicate dates as DD/MM/YYY)

Date of fracture: | Date of fracture delaying healing:

Date of fracture non-healing:

☐ Fracture to upper body (i.e., above waist) (Check all that apply)

- ☐ Cervical spine
- ☐ Clavicle
- ☐ Hand/metacarpal/phalange
- ☐ Head/face/skull
- ☐ Humerus
- ☐ Olecranon
- ☐ Radius
- ☐ Rib
- ☐ Scapula
- ☐ Shoulder
- ☐ Sternum
- ☐ Ulna
- ☐ Wrist/carpal
- ☐ Other

☐ Fracture to lower body (i.e., below waist) (Check all that apply)

- ☐ Ankle
- ☐ Fibula
- ☐ Hip
- ☐ Femur (Specify location: neck, subtrochanteric, mid shaft, etc)
- ☐ Tibia
- ☐ Pelvis
- ☐ Patella
- ☐ Foot/tarsal/metatarsal/phalange
- ☐ Other

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

- ☐ Severe trauma (e.g., falling from roof, motor vehicle accident)
- ☐ Minimal trauma (e.g., falling from standing position or less
- ☐ Non-traumatic

Characteristics of fracture (check all that apply)

- ☐ Comminuted
- ☐ Compound
- ☐ Pathologic
- ☐ Poor alignment
- ☐ Poor immobilization of segments
- ☐ Soft tissue injury
- ☐ Unknown

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AER#

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DENOSUMAB Core Questionnaire: **Fracture healing**

Treatment of adverse reaction (Please provide dates and indicate attachments if available)

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

- ☐ Casting
- ☐ Surgery
- ☐ Traction
- ☐ Non-surgical reduction
- ☐ Other
- ☐ Revision surgery (2nd surgery)

Did the fracture heal (union)?

☐ Yes ☐ No ☐ Unknown

If yes, date of union (DD/MM/YYYY)

If yes, was healing confirmed through imaging?

☐ Yes ☐ No ☐ Unknown

If yes, what diagnostic imaging? (Check all that apply)

☐ X-rays ☐ CT Scans ☐ MRI

If yes, is patient able to walk without assistance?

☐ Yes ☐ No ☐ Unknown

Medical history /Risk factors (Check all that apply, provide dates and attach relevant reports)

☐ Current smoker/tobacco use

3 of 4

Version 1.0

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AER#

Safety database number

Patient identifier

Study number

Above information to be filled by Fresenius Kabi.

DENOSUMAB Core Questionnaire: **Fracture healing**

☐ History or current corticosteroid use

☐ Prior fracture history

☐ Diabetes

Reporter Name:

Address:

City: State/ province:

Country: Postal code:

Email:

Phone (Include country code):

Signature:

Title: Date:

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Patient identifier

Study number

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DENOSUMAB Core Questionnaire: Malignancy Adverse Events

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Patient information (Please indicate dates as DD/MM/YYYY)

Patient initials

Gender: ☐ Female ☐ Male

Weight: ☐ lb ☐ kg

Date of event onset

Date of this report

Age at time of event:

Event reported term

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

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

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

If yes, date of prior cancer

Tumor stage, if known:

Primary site of malignancy?

Tumor stage

Tumor size (check which one applies)

☐ TX ☐ T0 ☐ Tis ☐ T1 ☐ T2 ☐ T3 ☐ T4

Tumor grade (check which one applies)

☐ GX ☐ G1 ☐ G2 ☐ G3

Localized (no regional involvement/no distant metastasis)? ☐ Yes ☐ No

(If yes, skip next 2 questions)

Lymph Node Involvement (Check which one applies)

☐ NX ☐ N1 ☐ N2 ☐ N3

Metastasis (check which one apllies)

☐ MX ☐ M0 ☐ M1

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AER# | Safety database number

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DENOSUMAB Core Questionnaire: Malignancy Adverse Events

Treatment of adverse reaction of malignancy

(check all that apply, please provide details and dates as DD/MM/YYYY)

Hospitalized	☐ Yes	☐ No	☐ Unknown
ICU admission?	☐ Yes	☐ No	☐ Unknown
Overall length of hospital stay	☐ ≤1 day	☐ >1 day or <=7 days	☐ > 7 days
Surgical treatment?	☐ Yes	☐ No	☐ Unknown
Chemotherapy (include biologics)?	☐ Yes	☐ No	☐ Unknown
Hormonal treatment?	☐ Yes	☐ No	☐ Unknown
Radiation treatment?	☐ Yes	☐ No	☐ Unknown
Bone marrow transplant?	☐ Yes	☐ No	☐ Unknown
If yes,	☐ autologous	☐ heterologous	
Was the malignancy treated with curative intention?	☐ Yes	☐ No	☐ Unknown
Further specifications			

Risk factors (check all that apply)

- ☐ Smoking
- ☐ Prior malignancy
- ☐ Positive family history (check all that apply)
  - ☐ Same cancer
  - ☐ Different cancer
- ☐ Prior therapeutic radiation exposure
- ☐ Environmental exposure (please specify)

Reporter Name:

Address:

City: State/ province:

Country: Postal code:

Email:

Phone (Include country code):

Signature:

Title: Date:

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AER# | Safety database number

Patient identifier | Study number

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DENOSUMAB Core Questionnaire: **Hypersensitivity**

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Patient information (Please indicate dates as DD/MM/YYYY)

Patient initials | Gender: ☐ Female ☐ Male | Date of event onset | Date of this report

Weight: ☐ lb ☐ kg

Event reported term

Age at time of event:

DENOSUMAB treatment information (Please indicate dates as DD/MM/YYYY)

DENOSUMAB indication

☐ Postmenopausal osteoporosis

☐ Bone loss from hormone ablation therapy
Please specify diagnosis

☐ Advanced cancer with bone metastasis
Please specify cancer

☐ Other (Please specify)

☐ Don't know

DENOSUMAB antibody testing performed
(Provide dates and results)

If not performed, do you have interest in antibody testing?

☐ Yes ☐ No

DENOSUMAB dosage

☐ 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

☐ Yes ☐ No ☐ Unknown

If yes, please specify

Doses of denosumab given after event began

☐ Yes ☐ No ☐ Unknown

If yes, date of first dose following start of event

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AER#

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Study number

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DENOSUMAB Core Questionnaire: **Hypersensitivity**

Signs and symptoms (Check all that apply)

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

Evaluations, diagnosis & laboratory measure (Please indicate and attach copy of report if available)

Diagnosis	Results/Units	Reference Range/Units	Date	Report attached Y	Report attached N
Results at baseline (prior to Denosumab treatment)					
Albumin					
ALP					
ALT					
AST					
Bilirubin					
BUN					
Calcium					
CBC with differential					
Cl-					
CrCl					
Eosinophils					
Hct					
Hgb					
K+					
Mg++					
Na+					
Platelets					
Phosphorus					
RBC					

continued...

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AER#	Safety database number
Patient identifier	**Study number**

Above information to be filled by Fresenius Kabi.

DENOSUMAB Core Questionnaire: **Hypersensitivity**

Diagnosis	Results/Units	Reference Range/Units	Date	Report attached Y	Report attached N
Results at baseline (prior to Denosumab treatment)					
Serum creatinine					
Total protein					
WBC					
Other (please specify)					

Evaluations, diagnosis & laboratory measure (Please indicate and attach copy of report if available)

Diagnosis	Results/Units	Reference Range/Units	Date	Report attached Y	Report attached N
Results at time of event					
Albumin					
ALP					
ALT					
AST					
Bilirubin					
BUN					
Calcium					
CBC with differential					
Cl-					
CrCl					
Eosinophils					
Hct					
Hgb					
K+					
Mg++					
Na+					
Platelets					
Phosphorus					
RBC					

continued...

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AER#

Safety database number

Patient identifier

Study number

Above information to be filled by Fresenius Kabi.

DENOSUMAB Core Questionnaire: **Hypersensitivity**

Diagnosis	Results/Units	Reference Range/Units	Date	Report attached Y	Report attached N
Results at baseline (prior to Denosumab treatment)					
Serum creatinine					
Total protein					
WBC					
Other (please specify)					

Treatment of adverse reaction of hypersensitivity

(Please provide dates and indicate attachments if available)

☐ ER corticosteroids

Route: ☐ IV ☐ Oral

☐ ER anti-histaminics

Route: ☐ IV only ☐ Oral only ☐ Both

☐ Required hospital admission

Overall length of hospital stay:

☐ ≤ 1 day ☐ > 1 day ☐ > 1 day or <= 7 days ☐ > 7 days

ICU admission ☐ Yes ☐ No ☐ Unknown

Overall length of ICU stay:

☐ ≤ 1 day ☐ > 1 day or < 7 days ☐ ≤ 7 days ☐ > 7 days

☐ In-hospital corticosteroids

Route: ☐ IV only ☐ Oral only ☐ Both

☐ In-hospital anti-histaminics

Route: ☐ IV only ☐ Oral only ☐ Both

☐ Other in-hospital treatment

IV vasopressors ☐ Yes ☐ No ☐ Unknown

Intubation/ mechanical ventilation ☐ Yes ☐ No ☐ Unknown

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

4 of 5

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DENOSUMAB Core Questionnaire: **Hypersensitivity**

Concomitant medications

☐ ACE inhibitors ☐ Cancer chemotherapy ☐ IV contrast ☐ Penicillamine

☐ Allopurinol ☐ Dapsone ☐ NSAIDS/aspirin ☐ Rifampin

☐ Anticonvulsants (check which apply)

☐ Carbamazepine ☐ Phenobarbital ☐ Phenytoin

☐ Antibiotics (check which apply)

☐ Beta-lactams including penicillin and cephalosporin ☐ Macrolides ☐ Quinolones ☐ Sulfonamides

Hypersensitivity event resolved ☐ Yes ☐ No ☐ Unknown

If yes, date (DD/MM/YYYY)

☐ Final diagnosis or etiology (inc. start date). Please send supporting documents for diagnosis

If yes, date (DD/MM/YYYY)

☐ Other consult report (Please indicate any attachments)

Reporter Name:

Address:

City: State/ province:

Country: Postal code:

Email:

Phone (Include country code):

Signature:

Title: Date:

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Annex 6 – Details of proposed additional risk minimisation activities.

Key messages of the additional risk minimisation measures

Patient Reminder Card

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

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

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