# EU Risk Management Plan
# Bomyntra (denosumab 120 mg)

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| **Marketing Authorization Holder (MAH)** | Fresenius Kabi Deutschland GmbH<br>Else-Kroener-Strasse 1<br>61352 Bad Homburg<br>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** | Updated as part of responses to D120 List of Questions |
| **Summary of significant changes in this RMP** | • Company code (FKS518) changed to brand name Bomyntra<br>• As committed in Response_Document_D120_Bomyntra (questions 128; #129, #130, and #131), update of the following sections to remove “Infection” and “Osteonecrosis outside the Jaw Including External Auditory Canal” as important potential risks, in line with the latest approved RMP for reference product:<br>- safety concerns sections<br>- Risk minimization measures (removal of “Infection” Follow-up questionnaire)<br>- Summary of risk minimization measures (removal of “Infection” and “Osteonecrosis outside the Jaw Including External Auditory Canal” from the description of routine risk minimisation measures by safety concern)<br>- Summary of the Risk Management Plan |
| **Other RMP versions under evaluation** | Not applicable |
| **Details of the currently approved RMP** | Not applicable |

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| **EU QPPV name** | Marcus Metternich |
| **EU QPPV signature** | |

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## 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 |
| CrCI | Creatinine clearance |
| CV | Cardiovascular |
| EMA | European Medicine Agency |
| EPAR | European Public Assessment Report |
| EU | European Union |
| GCTB | Giant cell tumour of bone |
| HALT | Hormone ablation therapy |
| IgG2 | Immunoglobulin G2 |
| IV | intravenous |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NPM | New primary malignancy |
| 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 |
| Q4W | Every 4 weeks |
| 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 |

| Abbreviation | Definition/Description |
|---|---|
| SmPC | Summary of Product Characteristics |
| SMQs | Standardized Medical Dictionary for Regulatory Activities Queries |
| SRE | Skeletal-related event |
| ULN | Upper Limit of Normal |
| US | United States |

# 1. Part I: Product(s) Overview

Product(s) Overview

| | |
|---|---|
| **Active substance(s)**<br>**(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)** | Bomyntra |
| **Marketing authorization procedure** | Centralised Procedure, Art. 10(4) similar biological application |
| **Brief description of the product** | Chemical class<br>Denosumab is a fully human immunoglobulin G2 (lgG) monoclonal antibody. |
| | Summary of mode of action<br>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<br>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<br>Refer to Xgeva RMP v 36.0, 11-Dec-2020<br>Refer to Prolia RMP v 31.0, 11-Jan-2023 |
| **Indication(s) (global)** | Current:<br>Not Applicable |

| | |
|---|---|
| | Proposed:<br>Prevention of skeletal-related events (SREs) (pathological fracture, radiation to bone, spinal cord compression, or surgery to bone) in adults with advanced malignancies involving bone.<br>Treatment of adults and skeletally mature adolescents with giant cell tumour of bone (GCTB) that is unresectable or where surgical resection is likely to result in severe morbidity. |
| **Dosages** | Current:<br>Not Applicable |
| | Proposed:<br>The recommended dose of Bomyntra for prevention of SREs is 120 mg administered as a single subcutaneous (SC) injection once every 4 weeks (Q4W) into the thigh, abdomen, or upper arm. Patients must be adequately supplemented with calcium and vitamin D.<br>The recommended dose of Bomyntra for treatment of adults or skeletally mature adolescents with GCTB is 120 mg Q4W administered as an SC injection, with additional 120 mg SC injections on days 8 and 15 of treatment of the first month of therapy. |
| **Pharmaceutical form(s) and strengths** | Current:<br>Not applicable |
| | Proposed:<br>- Solution for injection in vials. Each vial contains 120 mg of denosumab in 1.7 ml of solution (70 mg/mL).<br>- Solution for injection in pre-filled syringes. Each pre-filled syringe contains 120 mg of denosumab in 1.7 ml of solution (70 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 Bomyntra RMP is in line with the reference medicinal product, Xgeva®, solution for injection, Amgen, EU RMP version number 36.0, dated 11-Dec-2020.

### SI.1 Summary of Epidemiology of Bone Metastases From Solid Tumours

#### Incidence

Bone metastases are most commonly associated with cancers of the prostate, lung, and breast, with incidence rates as high as 75% of patients with metastatic disease (Carlin and Andriole 2000, Coleman 1997, Selvaggi and Scagliotti 2005, Viadana et al. 1973).

#### Prevalence

Bone metastases occur in more than 1.5 million patients with cancer worldwide (Coleman and Brown 2005). At autopsy nearly 70% of patients with breast or prostate cancer and roughly 40% of those dying with lung cancer have evidence of metastatic bone disease (Buijs and van der Pluijm 2009).

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

Bone metastases from solid tumours occur in both men and women; the incidence increases with age and higher stage at initial tumour diagnosis (Jensen et al. 2011, Nørgaard et al. 2010).

#### The main existing treatment options

In addition to systemic antitumor therapy, bisphosphonates are approved for patients with bone metastases to reduce the risk of developing SREs (Carlson et al. 2009, Hillner et al. 2003, Theriault et al. 2006, Warr et al. 2002).

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

Bone metastases are associated with significant skeletal morbidity (i.e., SREs, including fractures, radiation to bone, spinal cord compression, and surgery to bone) (Coleman 2006, Roodman 2004, Yonou et al. 2004).

Worldwide, approximately 1 million of 1.8 million people who die with breast, prostate, or lung cancer annually have bone metastases (Parkin et al. 2005).

#### Important comorbidities

- cardiovascular (CV) disease (Li et al. 2012, Lloyd-Jones et al. 1999, Nguyen et al. 2012);
- malignancy (Bergman et al. 2000, Chaplain et al. 2000, Curtis et al. 2006, Diamandidou et al. 1996, Dimopoulos et al. 2012, Evans et al. 2001, Liu et al. 2011, Mellemkjaer et al. 2006, Smith et al. 2003, Tanaka et al. 2001, Thellenberg et al. 2003, Volk and Pompe-Kirn 1997);

- infection (Li et al. 2012).

For comedications, Bomyntra is required to be administered in conjunction with adequate supplementation of calcium and vitamin D unless hypercalcemia is present.

Bomyntra is administered in conjunction with standard antineoplastic and/or supportive therapies as appropriate for the indicated populations.

## SI.2 Summary of Epidemiology of Giant Cell Tumour of Bone (GCTB)

### Incidence

Giant cell tumour of bone occurs in approximately 1 person per million per year (Liede et al. 2014). Each year, approximately 800, 800, 80, and 30 cases of GCTB are newly diagnosed in the United States (US), EU, Canada, and Australia, respectively.

### Prevalence

Giant cell tumour of bone accounts for 5% of all primary bone tumours and 20% of benign skeletal tumours in the Western world (Chakarun et al. 2013, Kim et al. 2012, Liede et al. 2014). As of 31 December 2013, an estimated 1581 to 2153 individuals had a diagnosis of benign GCTB within the previous 5 years (Liede et al. 2014). Similarly, the 3-year prevalence estimates in 2013 were 951 and 1295 individuals in the US (Liede et al. 2014).

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

Giant cell tumour of bone typically occurs in young adults. The median age at diagnosis (Swedish Cancer Registry data) is estimated at 34 years (interquartile range 25, 50 years), and the highest incidence per million is among individuals 20 to 39 years old (Amelio et al. 2016). Population-based data in Sweden and Japan estimate 39% to 55% of patients are diagnosed between age 20 and 39 years (Rockberg et al. 2015). Women comprise half or more of the affected population (Amelio et al. 2016, Rockberg et al. 2015).

### The Main Existing Treatment Options

Surgery can be curative if adequate resection of the tumour is performed (Malawer et al. 2011, Singer et al. 2011). For patients with unresectable GCTB, denosumab is presently the only approved therapy.

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

When left untreated, GCTB may progress to complete destruction of the affected bone and massive tumour formation.

Leggon *et al* reported that 21% of patients with GCTB of the pelvis or spine died during an average follow-up of 8.7 years (Leggon et al. 2004). Local recurrence rates vary from 10% to 40% post-surgery; most recurrences occur within 24 months of surgery (Becker et al. 2008, Blackley et al. 1999, Campanacci et al. 1987, Goldenberg et al. 1970, Hutter et al. 1962, Klenke et al. 2011, Lausten et al. 1996, Malek et al. 2006, Prosser et al. 2005).

**Important comorbidities**

For comedications, Bomyntra is required to be administered in conjunction with adequate supplementation of calcium and vitamin D unless hypercalcemia is present.

Bomyntra is administered in conjunction with standard antineoplastic and/or supportive therapies as appropriate for the indicated populations.

## SI.3 Summary of Epidemiology of Multiple Myeloma

### Incidence

The worldwide age standardized incidence of multiple myeloma is 1.5 cases per 100.000 persons per year overall (114.251 cases); 1.7 among men and 1.2 among women. Incidence per 100.000 per year ranges from 0.9 in Africa to 3.1 in the Americas and 3.2 in Europe (Ferlay et al. 2015).

### Prevalence

The 5-year prevalence is 4.4 per 100.000 adults (229.468 cases). The 5-year prevalence proportion per 100.000 ranges from 1.3 in Africa to 12.6 in Europe and 9.4 in the Americas (Ferlay et al. 2012).

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

The median age at diagnosis is approximately 70 years (Siegel et al. 2015). Multiple myeloma is more common in men than in women.

Black race, older age, and high body mass index are risk factors (Landgren and Weiss 2009, Wallin and Larsson 2011). Risk is 2.3 times higher in people with an affected first-degree relative compared with the general population (Frank et al. 2014).

Multiple myeloma risk is higher among individuals with systemic lupus erythematosus (Apor et al. 2014), autoimmune haemolytic anaemia (Shen et al. 2014), ankylosing spondylitis or pernicious anaemia (McShane et al. 2014), and lower in those with psoriasis (Shen et al. 2014).

### The Main Existing Treatment Options

Currently, bisphosphonates are the standard of care for the prevention of SREs in patients with multiple myeloma (Bird et al. 2011). The benefits of bisphosphonate treatment have been seen in patients with symptomatic multiple myeloma, even in the absence of evident bone lesions. However, bisphosphonates are known for adverse effects on renal function. Renal impairment is a common condition in patients with multiple myeloma which may increase risk of early death (Augustson et al. 2005, Knudsen et al. 1994).

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

Multiple myeloma is an incurable haematological neoplastic disorder characterized by uncontrolled proliferation of malignant plasma cells in the bone marrow (Durie 2006, MMRF 2021, Palumbo and Anderson 2011).

Clinically, multiple myeloma is characterized by hypercalcemia, renal impairment (Qian et al. 2017), anaemia, consequences of light chain deposition (amyloid), reduction in normal gamma globulins (immune paresis), and increased risk of infection. At diagnosis, up to 8% to 15% of patients are asymptomatic (Kyle and Rajkumar 2004), up to 96% have bone marrow involvement (Kyle et al. 2003), and 70 to 80% have bone lesions.

Typically, the severity of bone destruction correlates with disease burden (including SRE) and prognosis (Terpos et al. 2003). Osteoclast activity may also contribute to myeloma cell survival, growth, and resistance to apoptosis (Yaccoby et al. 2004). Thus, controlling further progression of myeloma bone disease may have direct consequences on both survival and quality of life for myeloma patients. Approximately 61% of multiple myeloma patients experience renal impairment, with 50% having chronic kidney disease (Qian et al. 2017).

Almost 47% of diagnosed patients survive 5-years or longer (Siegel et al. 2015). High-dose chemotherapy with autologous stem cell support and targeted treatments (e.g., thalidomide, bortezomib, and lenalidomide) have improved survival (Costa et al. 2016, Mateos and San Miguel 2013), with younger patients benefiting the most (Kristinsson et al. 2007, Kumar et al. 2014, Pulte et al. 2015, Schaapveld et al. 2010).

The age-standardized mortality rate is 1.0 per 100.000 persons per year, and ranges from 0.6 in Southeast Asia to 1.4 in Europe and 1.6 in the Americas (Ferlay et al. 2012).

**Important comorbidities**

- cardiovascular disease (Li et al. 2012, Lloyd-Jones et al. 1999, Nguyen et al. 2012);
- malignancy (Bergman et al. 2000, Chaplain et al. 2000, Curtis et al. 2006, Diamandidou et al. 1996, Dimopoulos et al. 2012, Evans et al. 2001, Liu et al. 2011, Mellemkjaer et al. 2006, Smith et al. 2003, Tanaka et al. 2001, Thellenberg et al. 2003, Volk and Pompe-Kirn 1997);
- infection (Li et al. 2012);
- renal impairment (Bladé and Rosiñol 2005, Dimopoulos et al. 2014, Gavriatopoulou et al. 2016, Qian et al. 2017).

For comedications, Bomyntra is required to be administered in conjunction with adequate supplementation of calcium and vitamin D unless hypercalcemia is present.

Bomyntra is administered in conjunction with standard antineoplastic and/or supportive therapies as appropriate for the indicated populations.

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

The similarity of FKS518 with the currently approved and marketed reference product, Xgeva (denosumab) has been investigated in a series of physicochemical and in vitro pharmacodynamic studies. Based on already available data, the analytical similarity between FKS518 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 FKS518.

Key safety findings from non-clinical studies and relevance to human usage (in line with the reference product, Amgen XGEVA RMP v36.0, 2020):

**Toxicity**

Reproductive Toxicity

Denosumab had no effect on female fertility or male reproductive organs in monkeys at exposures that were 9.5- to 16-fold higher, respectively, than the human exposure at 120 mg SC administered once Q4W.

In a study of cynomolgus monkeys dosed with denosumab during the period equivalent to the first trimester at area above the curve (AAC) exposures up to 10-fold higher than the human dose (120 mg Q4W), there was no evidence of maternal or foetal harm. In this study, foetal lymph nodes were not examined.

In another study of cynomolgus monkeys dosed with denosumab throughout pregnancy at AAC exposures 12-fold higher than the human dose (120 mg every 4-weeks), there were increased stillbirths and postnatal mortality; abnormal bone growth resulting in reduced bone strength, reduced haematopoiesis, and tooth malalignment; absence of peripheral lymph nodes; and decreased neonatal growth.

There was no evidence of maternal harm prior to labour; adverse maternal effects occurred infrequently during labour. Maternal mammary gland development was normal.

**Relevance to human usage**: 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.

Developmental Toxicity

Denosumab has been shown to be a potent inhibitor of bone resorption by inhibition of RANKL.

Adolescent primates dosed with denosumab at 2.8 and 15 times (10 and 50 mg/kg dose) the clinical exposure based on AAC had abnormal growth plates. 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 largely returned to normal; there were no adverse effects on tooth eruption; and minimal to moderate mineralization in multiple tissues was seen in one recovery animal.

In neonatal rats, inhibition of RANKL (target of denosumab therapy) was associated with inhibition of bone growth, altered growth plates, and inhibited tooth eruption, and these changes were partially reversible upon cessation of RANKL inhibition.

**Relevance to human usage**: Denosumab has not been established in paediatric patients other than skeletally mature paediatric patients with GCTB. Treatment with denosumab may impair bone growth in children with open growth plates and may inhibit eruption of dentition. 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.

### 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 numbers 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 XGEVA RMP v36.0, 2020)

| Criterion | Reason for exclusion | Is it to be included as missing information? (Yes/No) | Rationale |
|---|---|---|---|
| Severe, untreated hypocalcaemia | Pre-existing hypocalcaemia must be corrected prior to initiating therapy with denosumab. | 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. |
| Unhealed lesions from dental or oral surgery | While on treatment, invasive dental procedures should be performed only after careful consideration and be avoided in close proximity to denosumab administration. | No | It is a contraindication in the SmPC. |
| Patients with prior intravenous bisphosphonate treatment | For randomized, controlled trials, prior IV bisphosphonate treatment confounds the determination of efficacy. For all trials, it may increase the risk for safety events such as osteonecrosis of the jaw. | Yes | Not applicable |
| Current or prior bisphosphonate treatment | Use of bisphosphonates would interfere with the ability to assess denosumab's efficacy in clinical studies. | No | Data is available for 795 subjects in advanced cancer settings and an additional 19 subjects that received XGEVA from the multiple myeloma pivotal study who had previously received bisphosphonates.<br>Fresenius relied on reference product's study |

| Criterion | Reason for exclusion | Is it to be included as missing information? (Yes/No) | Rationale |
|---|---|---|---|
| | | | (denosumab) in cynomolgus monkeys transitioned from bisphosphonate therapy and 2 clinical studies of bisphosphonate-transition in bone loss settings. Results from these studies did not demonstrate an increased risk of skeletal adverse effects over the period exposed in patients who received denosumab following bisphosphonate use. Therefore, no special dosing recommendations or limitation of use for patients previously treated with bisphosphonates are considered necessary in the SmPC. |
| Exclusion Criteria for SRE (Multiple myeloma and Solid Tumour) only | | | |
| Patients with severe renal impairment Calculated creatinine clearance (CrCI) <30 mUmin. | Prescribing information for zoledronic acid states that use is not recommended in patients with severe renal impairment (defined as a CrCI <30 mUmin calculated using the Cockcroft-Gault equation). Because zoledronic acid was the comparator agent used in the 4 pivotal denosumab SRE Solid Tumour studies, subjects with a CrCI <30 mUmin were excluded from study participation. | No | Clinical study data for subjects with severe renal impairment (CrCI< 30 mUmin) including subjects receiving dialysis (317 subjects at time of initial registration and a clearance post registration pharmacology study of patients with CKD) have demonstrated an increased risk for hypocalcaemia including severe hypocalcaemia.<br>Changes in serum phosphorus and magnesium |

| Criterion | Reason for exclusion | Is it to be included as missing information? (Yes/No) | Rationale |
|---|---|---|---|
| | | | were small and there were few adverse events of hypophosphatemia or hypomagnesemia. Small increases in intact parathyroid hormone (iPTH) over time were seen in the CKD on dialysis group. |
| Exclusion Criteria for GCTB only | | | |
| Skeletally immature children and adolescents | Because treatment of juvenile rats and neonatal and adolescent cynomolgus monkeys resulted in widening of epiphyseal plates and because GCTB is rare in skeletally immature children and adolescents, skeletally immature subjects were excluded. | No | Denosumab is not indicated for treatment in children or skeletally immature adolescents. |
| Current receipt of other GCTB-specific treatment | Use of any other GCTB-specific treatment would interfere with the ability to assess denosumab's efficacy. | No | Because other treatments may interfere with the ability to assess denosumab efficacy, but it does not represent contraindication for the use of denosumab concomitantly with other putative treatments for GCTB (with the exception of bisphosphonates as indicated in the warnings and precautions section of the SmPC). |
| Known or suspected current diagnosis of underlying bone malignancy or brown tumour of bone | The presence of osteosarcoma or brown tumour of bone could interfere with the ability to assess denosumab's efficacy on GCTB. | No | Narrow indication (denosumab is not indicated for primary bone malignancy or brown tumour of bone). |

| Criterion | Reason for exclusion | Is it to be included as missing information? (Yes/No) | Rationale |
|---|---|---|---|
| Exclusion Criteria for SRE (Multiple Myeloma only) | | | |
| Non-secretory multiple myeloma based upon standard M-component criteria (ie, measurable serum / urine M-component) unless the baseline serum free-light chain level is elevated | Assessments of disease progression were based on International Myeloma Working Group criteria, which may include M protein or free-light chains. It is difficult to track disease progression based on standard assays for M protein or free-light chains in this population. | No | It is a diagnostic criterion, not a safety-related disease-specific criterion or contraindication. |

### 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.<br><br>In the Originator's clinical development program (Amgen XGEVA EU-RMP v36.0, 2020) there were 53 pregnancies from maternal exposure and pregnant partners of males and no cases of lactation 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.<br><br>The Originator's clinical development program (Amgen XGEVA EU-RMP v36.0, 2020) did not excluded patients with hepatic impairment (except for baseline alanine and aspartate aminotransaminases > 5X upper limit of normal [ULN], total bilirubin > 2X ULN) and no classification of liver functional status were collected. |
| Patients with renal impairment | Excluded from the FKS518 clinical development program.<br><br>The Originator's clinical development program (Amgen XGEVA EU-RMP v36.0, 2020) excluded patients with severe renal impairment from most registration studies in cancer populations. Clinical studies included 1055 subjects (1551.4 subject years) with moderate renal impairment and 36 subjects (49.5 subject years) had severe renal impairment or end-stage renal disease at entry. |
| Patients with cardiovascular impairment | No specific exclusion criteria were considered in the FKS518 clinical development program.<br><br>The Originator's clinical development program (Amgen XGEVA EU-RMP v36.0, 2020) did not consider specific exclusions regarding cardiovascular function and no classification of cardiac function status were collected. |
| lmmunocompromised patients | Excluded from the FKS518 clinical development program.<br><br>The Originator's clinical development program (Amgen XGEVA EU-RMP v36.0, 2020) did not consider specific exclusions with exception of human immunodeficiency virus (HIV) positive patients and no classification of liver functional status were collected. |
| Patients with a disease severity different from inclusion criteria in clinical trials | Not included in the clinical development program of both FKS518 and XGEVA. |
| Subpopulations carrying relevant genetic polymorphisms | No specific exclusions in both FKS518 and XGEVA clinical development programs. |

| Type of special population | Exposure |
|---|---|
| Population with relevant different ethnic origin | Not included in the clinical development program of both FKS518 and XGEVA. |
| Other | |
| Patients ≥75 years of age | Not included in the FKS518-001 study but considered for inclusion in the FKS518-002 study up to 85 years of age.<br>The Originator's clinical development program (Amgen XGEVA EU-RMP v36.0, 2020) included 1074 subjects (1625.9 subject years) ≥ 75 years and 168 subjects (254.9 subject-years) ≥85 years; no eligibility upper limit on age. |

## Part II: Module SV - Post-authorization experience

Not applicable. Bomyntra (denosumab 120 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 XGEVA (denosumab), the following are considered important risks:

- Important identified risks:

  1. Osteonecrosis of the Jaw;

  2. Atypical Femoral Fracture;

  3. Hypercalcemia several months after the last dose in patients with Giant Cell Tumour of Bone and In Patients with Growing Skeletons.

- Important potential risks:

  1. Cardiovascular events;

  2. Malignancy;

  3. Delay in Diagnosis of Primary Malignancy in Giant Cell Tumour of Bone;

  4. Hypercalcemia Several Months After the Last Dose in Patients Other Than Those With Giant Cell Tumour of Bone or Growing Skeletons.

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**<br>**Osteonecrosis of the Jaw** | |
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| 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 and postmarketing data of the reference product Amgen XGEVA (EU-RMP v36.0, 2020) and medical literature. |
| Characterization of the risk | *Frequency*<br>In Amgen's pooled pivotal SRE Solid Tumour studies, the subject incidence of positively adjudicated adverse events of ONJ was 1.8% in the denosumab group and 1.3% in the zoledronic acid group; the hazard ratio was 1.38 (95% Cl: 0.91, 2.11). In the SRE multiple myeloma study, the subject incidence of positively adjudicated adverse events of ONJ was 4.1% in the denosumab group and 2.8% in the zoledronic acid group; the hazard ratio was 1.47 (95% Cl: 0.88, 2.48) (Amgen XGEVA EU-RMP v36.0, 2020).<br>In Amgen's clinical trials, the incidence of ONJ was higher with longer duration of exposure (Amgen XGEVA® SmPC, May 2018). The incidence of ONJ remains of same magnitude in the SmPC current version (Amgen XGEVA® SmPC, Jul 2022)<br>In a non-interventional postmarketing observational Amgen's study of 2877 patients with cancer treated with XGEVA or zoledronic acid for SRE prevention, the incidence rates (95% Cl) of medically confirmed ONJ per 100 person-years were 3.0 (2.3, 3.7) in the XGEVA inception cohort, 1.0 (0.6, 1.5) in the zoledronic acid inception cohort, and 4.3 (2.8, 6.3) in the XGEVA-switch cohort (this cohort included patients who switched to |

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| | XGEVA after having started antiresorptive therapy with bisphosphonates for SRE prevention of no more than 2 years' net duration.<br><br>*Severity*<br><br>Most events leading to adjudication as ONJ were assessed as moderate to severe. Life-threatening events have been reported (Amgen XGEVA EU-RMP v36.0, 2020).<br><br>*Reversibility*<br><br>In general, ONJ events are clinically reversible. The majority of ONJ cases resolve with denosumab treatment interruption or discontinuation. Surgical treatment may be required; bone resection is not usually necessary.<br><br>*Long-term outcomes*<br><br>No data on long-term outcomes are available.<br><br>*Impact on Quality of Life*<br><br>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 associated with ONJ include the use of antiresorptive (particularly aminobisphosphonates delivered by intravenous [IV] dosing), older age, poor dental hygiene, periodontal disease, invasive dental procedures, trauma from poorly fitting dentures, malignancy, chemotherapy (including antiangiogenesis agents such as bevacizumab), radiation to head and neck, corticosteroids, hypercoagulable state secondary to underlying malignancy, smoking and vascular insufficiency due to thrombosis (Almazrooa and Woo 2009, Estilo et al. 2008, 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. Good oral hygiene practices should be maintained during treatment with denosumab and dental health should be monitored. |
| 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. |

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| Public health impact | Significant public health impact is not expected based on the relative frequency observed in clinical trials and with the observations that most ONJ events appear to be moderate to severe in severity and resolve without requiring extensive surgical treatment. |
| **Important identified risk**<br>**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 and postmarketing data of the reference product Amgen XGEVA (EU-RMP v36.0, 2020) and medical literature. |
| Characterization of the risk | *Frequency*<br>In a comprehensive evaluation of Amgen's denosumab 120 mg clinical trials, 15 subjects experienced 17 events meeting the American Society for Bone and Mineral Research criteria for AFF. This corresponds to 0.2% (15 of 8342) of all subjects who received at least 1 dose of denosumab (Similar results are observed when consideration is limited to studies utilizing monthly dosing throughout [0.1%, 6 subjects with AFF in 6101 subjects]). All of these adjudicated events of AFF occurred in subjects who received denosumab 120 mg for at least 4 years corresponding to 0.7% (15 of the 2228) of subjects who were followed for 4 or more years (Amgen XGEVA EU-RMP v36.0, 2020).<br>In the Amgen's clinical trial program, AFF has been reported uncommonly in patients treated with XGEVA 120 mg and the risk increased with longer duration of treatment. Events have occurred during treatment and up to 9 months after treatment was discontinued (Amgen XGEVA EU-RMP v36.0, 2020).<br>*Severity*<br>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. |

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| | *Reversibility*<br>It is unknown if the pathophysiological mechanism(s) contributing to the development of AFF are reversible after treatment is discontinued.<br>*Long-term outcomes*<br>No data on long-term outcomes are available.<br>*Impact on Quality of Life*<br>As with other hip fractures, AFF can cause short-term or long-term disability. Some data suggests that healing of AFF may be more prolonged than a typical femoral fracture (Bubbear 2016, Unnanuntana et al. 2013). |
| Risk group or risk factors | Long-term anti resorptive 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, rheumatoid arthritis, 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 balance of the product | The risk of AFF events has been considered in the product benefit-risk assessment. In light of the product labelling that has been proposed to minimize this risk, the overall benefit-risk balance is considered to be positive. |
| Public health impact | Based on the frequency of AFF, the size of the indicated populations, and usage patterns of denosumab in clinical practice, no significant additional public health impact is expected. |
| **Important identified risk**<br>**Hypercalcemia Several Months After the Last Dose in Patients With Giant Cell Tumour of Bone and in Patients With Growing Skeletons** | |
| Potential mechanism | The mechanism(s) of hypercalcemia several months after the last dose of denosumab in patients with GCTB and in patients with a growing skeleton are not well characterized, but may be a consequence of the following, alone, or in combination:<br>Denosumab treatment and resultant RANK/RANKL pathway inhibition in adults with giant-cell containing lesions such as GCTB leads to histopathologic evidence of a dramatic decrease in osteoclast-like giant cells which is complemented by woven bone formation and calcification |

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| | within the tumours and even at sites of distant metastases (Branstetter et al. 2012, Ghermandi et al. 2016, Yamagishi et al. 2016). It is possible this calcium could serve as a depot that is mobilized with reactivation of tumour-associated, RANKL driven giant cell mediated osteolysis following cessation of XGEVA (Amgen XGEVA EU-RMP v36.0, 2020).<br>• Hypercalcemia may result from rapid resorption of retained primary spongiosa in a skeleton with active endochondral ossification such as in patients with a growing skeleton. The rate of endochondral ossification and duration of exposure to denosumab would determine the amount of accumulated primary spongiosa that could influence the magnitude of resorptive response (mechanostat-driven) and release of calcium from the skeleton either near the growth plates (as can be the case with the young adult and adolescent patients) or from the giant cell tumours themselves that have partially ossified in the cases of the adult patients with tumour recurrence via an autocrine/paracrine mechanism (Cowan et al. 2011).<br>• The magnitude of the resorptive response following treatment withdrawal in the patients with GCTB and in those with an immature skeleton could be dictated by the normal high rate of bone turnover within the GCTB lesion or in the growing skeleton of young patients.<br>The response of the osteoclast lineage to loss of inhibition of osteoclastogenesis may be intrinsically more robust in young individuals or may be affected by intratumor signalling pathways (e.g., parathyroid hormone-related protein) in GCTB (Amgen XGEVA EU-RMP v36.0, 2020). |
| Evidence source(s) and strength of evidence | The source of information is clinical/safety and postmarketing data of the reference product Amgen XGEVA (EU-RMP v36.0, 2020) and medical literature. |
| Characterization of the risk | *Frequency*<br>Based on the 4 relevant clinical trial case reports (2 adults and 2 adolescents) identified from a completed Amgen's clinical study of subjects with GCTB (526 subjects having received at least 1 dose of XGEVA), the frequency of hypercalcemia in patients with GCTB following discontinuation of XGEVA is 0.8 events per 100 subjects which corresponds to an uncommon frequency (≥0.1 and <1 event per 100 subjects).<br>In addition, clinically significant cases of post-treatment hypercalcemia have been identified from literature case reports of denosumab use in |

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| | paediatric patients for unapproved indications such as fibrous dysplasia, aneurysmal bone cysts, and juvenile Paget's disease.<br><br>*Severity*<br><br>In the Amgen's GCTB study, the events of hypercalcemia in the 4 subjects were considered grade 2, 3, or 4 in severity. All subjects had acute renal injury and all were hospitalized. Three of 4 subjects had more than 1 event. The severity of the events in the postmarketing literature case reports appears qualitatively similar (Amgen XGEVA EU-RMP v36.0, 2020).<br><br>*Reversibility*<br><br>Hypercalcemia is reversible with appropriate supportive therapy.<br><br>*Long-term outcomes*<br><br>No data on long-term outcomes are available.<br><br>*Impact on Quality of Life*<br><br>Patients may present with severe hypercalcemia requiring hospitalization. Patients who experience hypercalcemia may develop complications such as acute renal injury. |
| Risk group or risk factors | Patients with GCTB and young patients with growing skeletons following discontinuation of denosumab. In general, the most common cause of hypercalcemia in humans is hyperparathyroidism, particularly among women and individuals aged 65 years or older (Minisola et al. 2015). Hyperthyroidism and rhabdomyolysis associated with renal failure also increase the risk of hypercalcemia, as does the ingestion of large of amounts of calcium through dairy products or more recently liberal use of calcium supplements (Machado et al. 2015, Minisola et al. 2015). |
| Preventability | No preventive measures are known. Monitor patients for signs and symptoms of hypercalcemia and treat appropriately. Periodic serum calcium assessments should be given to at-risk patients as clinically indicated. The need for calcium and vitamin D supplementation should be reassessed if denosumab is discontinued. |
| Impact on the risk-benefit balance of the product | The risk of hypercalcemia events several months after the last dose in patients with GCTB and in patients with growing skeletons has been considered in the product benefit-risk assessment. In light of the product labelling that has been proposed to minimize this risk, the overall benefit-risk balance is considered to be positive. |
| Public health impact | No significant public health impact is expected as hypercalcemia several months after the last dose in patients with GCTB occurs uncommonly and GCTB is a rare tumour. Off-label use of denosumab in paediatric patients appears to be limited to rare conditions for which there is significant unmet medical need. |

| **Important potential risk**<br>**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 | The risk of CV events is a safety concern based on the epidemiological association between OPG levels and CV disease in man. Amgen's clinical data have not substantiated a cause-and-effect between OPG and atherosclerotic processes nor between denosumab or inhibition of RANKL and undesirable CV outcomes (Amgen XGEVA EU-RMP v36.0, 2020). |
| Characterization of the risk | *Frequency*<br>In Amgen's pooled pivotal SRE Solid Tumour studies, subject incidence of CV adverse events was 29.7% in both treatment groups; the hazard ratio was 0.98 (95% Cl: 0.89, 1.08).<br>In a Amgen's pivotal study with denosumab 120 mg Q4W in subjects with CRPC, the subject incidence of CV adverse events was 33.1 % in the denosumab group and 27.0% in the placebo group; the hazard ratio was 1.23 (95% Cl: 1.02, 1.49).<br>In the Amgen's SRE multiple myeloma study, the subject incidence of adverse events of cardiac disorders was 11.6% in the denosumab group and 13.5% in the zoledronic acid group; the hazard ratio was 0.85 (95% Cl: 0.65, 1.12). The subject incidence of adverse events of vascular disorder was 20.9% in the denosumab group and 19.8% in the zoledronic acid group; the hazard ratio was 1.07 (95% Cl: 0.86, 1.31) (Amgen XGEVA EU-RMP v36.0, 2020).<br>*Severity*<br>The majority of CV events were mild to moderate. Life-threatening and fatal events have been reported (Amgen XGEVA EU-RMP v36.0, 2020).<br>*Reversibility*<br>No data on reversibility are available.<br>*Long-term outcomes*<br>No data on long-term outcomes are available. |

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| | *Impact on Quality of Life*<br>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 Amgen's denosumab development program comprises studies of older subject populations (e.g., osteoporosis, cancer) that are likely to have a higher incidence of pre-existing CV conditions and, thus, a higher incidence of CV toxicities than that of the general population (Hak et al. 2000, Schulz et al. 2004).<br>Risk factors for atherosclerosis include age, gender, ethnicity, family history, elevated lipid levels, cigarette smoking, hypertension, diabetes, and concomitant medications, including antipsychotic agents and cyclooxygenase-2 (COX-2) inhibitors (Murphy and Dargie 2007, Smith et al. 2004). |
| Preventability | Based on Amgen's clinical data to date, denosumab has not been associated with an increased incidence or severity of CV adverse effects; therefore, no preventive measures are defined. Patients with potential CV events should be managed according to usual standards of care. |
| Impact on the risk-benefit balance of the product | The risk of CV events has been considered in the product benefit-risk assessment, and the overall benefit-risk balance is considered to be positive. |
| Public health impact | Significant public health impact on CV disease severity or incidence is not expected based on the information from denosumab clinical studies in the advanced cancer and postmenopausal osteoporosis (PMO)/hormone ablation therapy (HALT) settings. |
| **Important potential risk**<br>**Malignancy** | |
| Potential mechanism | The risk of malignancy is a theoretical concern that RANKL inhibition may lead to an increased risk for a new primary malignancy (NPM) by impairing immune surveillance mechanisms. |
| Evidence source(s) and strength of evidence | Imbalance is observed in the NPM events between the zoledronic acid and XGEVA treatment groups in Amgen's pivotal clinical studies. The results of an Amgen's postmarketing retrospective cohort study, showed NPM incidence rates for XGEVA were generally lower than those for zoledronic acid in unadjusted analyses, suggesting no obvious excess risk associated with XGEVA (Amgen XGEVA EU-RMP v36.0, 2020). |

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| Characterization of the risk | *Frequency*<br><br>In the primary, double-blind treatment phases of 4 phase 3 active-controlled Amgen's clinical trials in patients with advanced malignancies involving bone, NPM was reported in 54/3,691 (1.5%) of patients treated with XGEVA (median exposure of 13.8 months; range: 1.0 to 51.7) and 33/3,688 (0.9%) of patients treated with zoledronic acid (median exposure of 12.9 months; range: 1.0 to 50.8). The cumulative incidence at 1 year was 1.1% for denosumab and 0.6% for zoledronic acid, respectively.<br><br>In the Amgen's SRE multiple myeloma study, the subject incidence of adverse events of NPM was 2.6% in the denosumab group and 1.4% in the zoledronic acid group; the hazard ratio was 1.81 (95% CI: 0.90, 3.66). Subjects who had new malignancies in this study generally had underlying risk factors for malignancy and no pattern was apparent in the types of new primary malignancies.<br><br>In Amgen's clinical study in GCTB, based on medical review and a data cut-off date of the final analysis of 15-Aug-2018, a total of 20 subjects (3.8%; N = 526) developed new malignancy in GCTB. Of these 20 subjects, 9 subjects developed new malignancies that were unrelated to GCTB: 2 events (0.4%) of ductal breast carcinoma and single events of each, adenocarcinoma of colon, breast cancer stage I, neoplasm, oesophageal adenocarcinoma, osteosarcoma, papillary thyroid cancer, renal cancer, rhabdomyosarcoma, and thyroid cancer. A total of 11 subjects (2.1%) developed new malignancy in GCTB: 5 subjects were deemed to have had primary malignant GCTB, 5 subjects were assessed to have had sarcomatous transformation, and 1 subject had secondary malignant GCTB (post-radiation).<br><br>In an Amgen's retrospective observational cohort study of 9,710 patients with bone metastases from breast, prostate, or lung cancer treated with XGEVA or IV zoledronic acid, the overall rate of NPM for the breast cancer cohort was 11.5 per 1000 person-years (PY) of follow-up in the XGEVA group and 16.2 per 1000 PY in the zoledronic acid group; for the prostate cancer cohort was 19.6 per 1000 PY in the XGEVA group and 20.1 per 1000 PY in the zoledronic acid group; and for the lung cancer cohort was 9.5 per 1000 PY in the XGEVA group and 11.5 per 1000 PY in the zoledronic acid group.<br><br>The 3-year cumulative incidence of NPM for the breast cancer cohort was 0.022 (95% CI: 0.014, 0.035) in the XGEVA group and 0.032 (95% CI: 0.023, 0.045) in the zoledronic acid group; for the prostate cancer cohort was 0.034 (95% CI: 0.026, 0.044) in the XGEVA group and 0.036 (95% CI: 0.026, 0.049) in the zoledronic acid group; and for the lung cancer cohort was 0.007 (95% CI: 0.004, 0.012) in the XGEVA group and 0.008 (95% CI: 0.005, 0.014) in the zoledronic acid group (Amgen XGEVA EU-RMP v36.0, 2020). |

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| | *Severity*<br>Not applicable.<br>*Reversibility*<br>No data on reversibility are available.<br>*Long-term outcomes*<br>No data on long-term outcomes are available.<br>*Impact on Quality of Life*<br>Malignancy is typically disabling and may require surgery, chemotherapy, and/or radiotherapy. |
| Risk group or risk factors | General factors for increasing risk of NPM include advancing age, diet, cigarette smoking, excessive ethanol consumption, and numerous environmental toxins. In addition, advanced cancer populations are at increased risk for NPM because of their existing malignancy, possible genetic predisposition, and exposure to chemotherapy and radiation treatment. |
| Preventability | Second malignant neoplasms have become increasingly recognized and current recommendations include vigilance for these cancers in adult cancer survivors. |
| Impact on the risk-benefit balance of the product | The risk of malignancy events has been considered in the product benefit-risk assessment. In light of the product labelling 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 based on the information from studies in the PMO/HALT and advanced cancer settings. |
| **Important potential risk**<br>**Delay in Diagnosis of Primary Malignancy in Giant Cell Tumour of Bone** | |
| Potential mechanism | Due to well described sampling error at the time of GCTB diagnosis, primary malignancy in giant cell tumour of bone (PMGCTB) may be missed and benign GCTB may be presumed. Based on the mechanism of action and pathology of GCTB, denosumab is only expected to treat benign GCTB. However, there was a theoretical concern that treatment of an undiagnosed PMGCTB with denosumab could delay the diagnosis of PMGCTB. |
| Evidence source(s) and | The risk of delay in diagnosis of PMGCTB is a regulatory concern based on the difficulties in diagnosing PMGCTB in Amgen's studies (Amgen XGEVA EU-RMP v36.0, 2020). |

<table>
<tr><td>strength of evidence</td><td></td></tr>
<tr><td>Characterization of the risk</td><td>Frequency<br>In Amgen’s clinical studies in GCTB, based on medical review, 11 subjects (2.1%; N=523) had GCTB bone malignancies. Of these, 5 subjects (1.0%) had PMGCTB (Amgen XGEVA EU-RMP v36.0, 2020).<br><table><tr><th></th><th>Time to PMGCTB</th></tr><tr><td>Number of cases</td><td>5</td></tr><tr><td>Mean time (Q1, Q3) to malignancy (months)[a]</td><td>19.12 (11.99, 24.18)</td></tr><tr><td>Median (min, max) denosumab exposure (months)</td><td>8.44 (2.8, 14.8)</td></tr></table>[a]Time from diagnosis of GCTB to diagnosis of malignancy of GCTB<br>Severity<br>Not applicable.<br>Reversibility<br>Not applicable.<br>Long-term outcomes<br>No data on long-term outcomes are available.<br>Impact on Quality of Life<br>Malignancy is typically disabling and may require surgery, chemotherapy, and/or radiotherapy.</td></tr>
<tr><td>Risk group or risk factors</td><td>Patients with GCTB are known to be at risk for PMGCTB.</td></tr>
<tr><td>Preventability</td><td>No preventive measures are known.</td></tr>
<tr><td>Impact on the risk-benefit balance of the product</td><td>The risk of delay in diagnosis of PMGCTB events has been considered in the product benefit-risk assessment. In light of the product labelling that has been proposed to minimize this risk, the overall benefit-risk balance is considered to be positive.</td></tr>
<tr><td>Public health impact</td><td>Given that GCTB is very rare condition, no impact on public health is expected.</td></tr>
<tr><td colspan="2">Important potential risk<br>Hypercalcemia Several Months After the Last Dose in Patients Other Than Those With Giant Cell Tumour of Bone or Growing Skeletons</td></tr>
</table>

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| Potential mechanism | The pathogenesis of hypercalcemia several months after the last dose in patients other than those with GCTB or growing skeletons may be a consequence of the transient increase in bone turnover activity. Upon cessation of denosumab, the disinhibition of RANKL allows for terminal differentiation and activation of osteoclasts, which were suppressed during treatment. In patients with underlying causes for calcium dyscrasias (i.e., subclinical hyperparathyroidism), denosumab discontinuation, with its transient increase in bone remodelling and accompanying release of bone mineral, could theoretically be associated with transient hypercalcemia in susceptible individuals if the normal homeostatic mechanism regulating serum calcium are not appropriately maintained. |
| Evidence source(s) and strength of evidence | Hypercalcemia several months after the last dose in patients other than those with GCTB or growing skeletons is a theoretical concern based on the identified risk in other specific populations, GCTB, and paediatric populations (Amgen XGEVA EU-RMP v36.0, 2020). |
| Characterization of the risk | *Frequency*<br>Cases of hypercalcemia in the off-treatment period have been reported in Amgen's clinical studies, but given the disease state of the subjects, as well as other confounding factors, the occurrence of hypercalcemia in patients other than those with GCTB or with growing skeletons cannot be attributed to discontinuation of XGEVA based on available information. As the mechanism for the identified risk in the susceptible populations is not well understood, a theoretical risk remains in other patient groups (Amgen XGEVA EU-RMP v36.0, 2020).<br>*Severity*<br>Not applicable.<br>*Reversibility*<br>No data on reversibility are available.<br>*Long-term outcomes*<br>No data on long-term outcomes are available.<br>*Impact on Quality of Life*<br>Patients may present with severe hypercalcemia requiring hospitalization. Patients who experience hypercalcemia may develop complications such as acute renal injury. |
| Risk group or risk factors | Patients other than those with GCTB or growing skeletons following cessation of denosumab. |

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

### SVII.3.2 Presentation of the missing information

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| **Use in Patients With Prior Intravenous Bisphosphonate Treatment** | |
| Evidence source | The incidence of ONJ in patients with prior IV bisphosphonate use was similar to that of patients who only received XGEVA in an Amgen's clinical study. No notable association was evident between ONJ and prior use of bisphosphonates (Amgen XGEVA RMP v36.0, 2020). |
| Population in need of further characterization | There is information from Amgen's studies in patients with cancer showing that there is no increased risk of serious complications caused by bone metastases in patients who received XGEVA following treatment with bisphosphonates. However, more information is needed (Amgen XGEVA RMP v36.0, 2020). |
| **Safety With Long-Term Treatment and With Long-Term Follow-up After Treatment in Adults and Skeletal Mature Adolescents with GCTB** | |
| Evidence source | The overall safety profile of XGEVA in the completed Amgen's study was similar to the safety profile of XGEVA observed in the treatment of subjects with advanced cancer and bone metastases (Amgen XGEVA RMP v36.0, 2020). |
| Population in need of further characterization | Information on safety with long-term treatment and with long-term follow-up in adults or adolescents with GCTB will be monitored by routine pharmacovigilance activities. |
| **Off-label Use in Patients With GCTB That is Resectable Where Resection is Unlikely to Result in Severe Morbidity** | |
| Evidence source | No formal studies have been completed to determine denosumab effect on off-label use in patients with GCTB that is resectable where resection is unlikely to result in severe morbidity. |

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

## Part II: Module SVIII - Summary of safety concerns

Table 7. Details of important identified and potential risks of FKS518

| **Safety Concerns** | |
|---|---|
| Important identified risks | • Osteonecrosis of the Jaw<br>• Atypical Femoral Fracture<br>• Hypercalcemia several months after the last dose in patients with Giant Cell Tumour of Bone and In Patients with Growing Skeletons |
| Important potential risks | • Cardiovascular events<br>• Malignancy<br>• Delay in Diagnosis of Primary Malignancy in Giant Cell Tumour of Bone<br>• Hypercalcemia Several Months After the Last Dose in Patients Other Than Those With Giant Cell Tumour of Bone or Growing Skeletons |
| Missing information | • Use in Patients with Prior Intravenous Bisphosphonate Treatment<br>• Safety With Long-Term Treatment and With Long Term Follow-up After Treatment in Adults and Skeletal Mature Adolescents with GCTB<br>• Off Label Use in Patients with GCTB That is Resectable Where Resection is Unlikely to Result in Severe Morbidity |

# 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 Bomyntra 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 Bomyntra related to some of the risks:

| Follow-up Questionnaire | Safety concern(s) | Purpose |
|---|---|---|
| Osteonecrosis of the Jaw | Osteonecrosis of the Jaw | To monitor the reporting rate and nature of ONJ in patients treated with Bomyntra in the postmarketing environment. |
| Postmarketing reports of potential atypical fracture | Atypical Femoral Fracture | To monitor the reporting rate and nature of AFF in patients treated with Bomyntra 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 Bomyntra. 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 Bomyntra.

# 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:**<br>**Osteonecrosis of the Jaw** | **Routine risk communication:**<br>SmPC<br>• Section 4.3, Section 4.4, Section 4.8, Section 5. 1.<br>Patient Information leaflet (PIL)<br>• Section 2, Section 4.<br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br>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.<br>**Other risk minimization measures beyond the Product Information:**<br>Medicine's legal status: prescription only medicine. |
| **Important identified risk:**<br>**Atypical Femoral Fracture** | **Routine risk communication**:<br>SmPC<br>• Section 4.4, Section 4.8.<br>PIL<br>• Section 2, Section 4.<br>**Routine risk minimization activities recommending specific clinical measures to address the risk**:<br>Recommendation for reporting new or unusual thigh, hip, or groin pain is included Section 4.4 of SmPC.<br>**Other risk minimization measures beyond the Product Information**:<br>Medicine's legal status: prescription only medicine. |

| Safety concern | Routine risk minimization activities |
|---|---|
| **Important identified risk:**<br>**Hypercalcemia several months after the last dose in patients with Giant Cell Tumour of Bone and In Patients with Growing Skeletons** | **Routine risk communication:**<br>SmPC<br>• Section 4.4, Section 4.8.<br>PIL<br>• Section 2, Section 4.<br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br>Recommendations for monitoring the patients for signs and symptoms of hypercalcaemia after discontinuation of Bomyntra treatment are included in Section 4.4 of SmPC and Section 4 of the PIL.<br>**Other risk minimization measures beyond the Product Information:**<br>Medicine's legal status: prescription only medicine. |
| **Important potential risk:**<br>**Cardiovascular events** | **Routine risk communication:**<br>Not applicable.<br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br>None.<br>**Other risk minimization measures beyond the Product Information:**<br>Medicine's legal status: prescription only medicine. |
| **Important potential risk:**<br>**Malignancy** | **Routine risk communication:**<br>SmPC<br>• Section 4.4, Section 4.8, Section 5.1<br>PIL<br>• Section 4<br>**Routine risk minimization activities recommending specific clinical measures to address the risk:** |

| Safety concern | Routine risk minimization activities |
|---|---|
| | Recommendations for monitoring the patients for radiological signs of malignancy, new malignancy, or osteolysis are included in Section 4.4 of SmPC.<br>**Other risk minimization measures beyond the Product Information:**<br>Medicine's legal status: prescription only medicine. |
| **Important potential risk:**<br>**Delay in Diagnosis of Primary Malignancy in Giant Cell Tumour of Bone** | **Routine risk communication:**<br>Not applicable.<br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br>None.<br>**Other risk minimization measures beyond the Product Information:**<br>Medicine's legal status: prescription only medicine. |
| **Important potential risk:**<br>**Hypercalcemia Several Months After the Last Dose in Patients Other Than Those With Giant Cell Tumour of Bone or Growing Skeletons** | **Routine risk communication:**<br>Not applicable.<br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br>None.<br>**Other risk minimization measures beyond the Product Information:**<br>Medicine's legal status: prescription only medicine. |
| **Missing information:**<br>**Use in Patients with Prior Intravenous Bisphosphonate Treatment** | **Routine risk communication:**<br>SmPC<br>• Section 4.5, Section 5.1<br>PIL<br>• Section 2<br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br>None.<br>**Other risk minimization measures beyond the Product Information:** |

| Safety concern | Routine risk minimization activities |
|---|---|
| | Medicine's legal status: prescription only medicine. |
| **Missing information:**<br>**Safety With Long-Term Treatment and With Long-Term Follow-up After Treatment in Adults and Skeletal Mature Adolescents with GCTB** | **Routine risk communication:**<br>Not applicable.<br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br>None.<br>**Other risk minimization measures beyond the Product Information:**<br>Medicine's legal status: prescription only medicine. |
| **Missing information:**<br>**Off Label Use in Patients with GCTB That is Resectable Where Resection is Unlikely to Result in Severe Morbidity** | **Routine risk communication:**<br>Not applicable.<br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br>None.<br>**Other risk minimization measures beyond the Product Information:**<br>Medicine's legal status: prescription only medicine. |

## V.2 Additional risk minimization measures

Table 9 Additional risk minimization measures by safety concern

| **Important identified risk**<br>**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 | The purpose of the Patient Reminder Cards is to remind patients about important safety information that they need to be aware of before and |

| | |
|---|---|
| minimization activity | during treatment with denosumab (Bomyntra) injections for cancer-related conditions, including:<br>• To tell their doctor/nurse if they have any problems with their mouth or teeth before starting treatment;<br>• To maintain good oral hygiene and receive routine dental check-ups during treatment;<br>• To inform their doctor and tell their dentist that they are being treated with denosumab (Bomyntra) if they are under dental treatment or will undergo dental surgery;<br>• To contact their doctor and dentist immediately if they experience any problems with their mouth or teeth such as loose teeth, pain or swelling, non-healing of sores or discharge. |
| Target audience and planned distribution path | 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 PSURs.<br>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 and web downloads 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 Bomyntra. |

### 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:**<br>**Osteonecrosis of the Jaw** | **Routine risk minimization measures:**<br>• SmPC: Section 4.3, Section 4.4, Section 4.8, section 5.1 | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** |

| Safety concern | Risk minimization measures | Pharmacovigilance activities |
|---|---|---|
| | • PIL: Section 2, Section 4<br>**Other risk minimization measures**<br>• Legal status: prescription only medicine<br>**Additional risk minimization measures:**<br>• Patient Reminder Card | • Denosumab core questionnaire - Osteonecrosis of the Jaw<br>**Additional pharmacovigilance activities:**<br>• None |
| **Important identified risk:**<br>**Atypical Femoral Fracture** | **Routine risk minimization measures:**<br>• SmPC: Section 4.4, Section 4.8<br>• PIL: Section 2, Section 4<br>**Other risk minimization measures**<br>• Legal status: prescription only medicine<br>**Additional risk minimization measures:**<br>• None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>• Denosumab core questionnaire – Postmarketing reports of potential atypical fracture<br>**Additional pharmacovigilance activities:**<br>• None |
| **Important identified risk:**<br>**Hypercalcemia several months after the last dose in patients with Giant Cell Tumour of Bone and In Patients with Growing Skeletons** | **Routine risk minimization measures:**<br>• SmPC: Section 4.4, Section 4.8<br>• PIL: Section 2, Section 4<br>**Other risk minimization measures**<br>• Legal status: prescription only medicine<br>**Additional risk minimization measures:**<br>• None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>• None<br>**Additional pharmacovigilance activities:**<br>• None |
| **Important potential risk:**<br>**Cardiovascular events** | **Routine risk minimization measures:**<br>• Not applicable<br>**Other risk minimization measures**<br>• Legal status: prescription only medicine | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>• None |

| Safety concern | Risk minimization measures | Pharmacovigilance activities |
|---|---|---|
| | **Additional risk minimization measures:**<br>• None | **Additional pharmacovigilance activities:**<br>• None |
| **Important potential risk:**<br>**Malignancy** | **Routine risk minimization measures:**<br>• SmPC: Section 4.4, Section 4.8, Section 5.1<br>• PIL: Section 4<br>**Other risk minimization measures**<br>• Legal status: prescription only medicine<br>**Additional risk minimization measures:**<br>• None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>• None<br>**Additional pharmacovigilance activities:**<br>• None |
| **Important potential risk:**<br>**Delay in Diagnosis of Primary Malignancy in Giant Cell Tumour of Bone** | **Routine risk minimization measures:**<br>• None<br>**Other risk minimization measures**<br>• Legal status: prescription only medicine<br>**Additional risk minimization measures:**<br>• None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>• None<br>**Additional pharmacovigilance activities:**<br>• None |
| **Important potential risk:**<br>**Hypercalcemia Several Months After the Last Dose in Patients Other Than Those With Giant Cell Tumour of Bone or Growing Skeletons** | **Routine risk minimization measures:**<br>• None<br>**Other risk minimization measures**<br>• Legal status: prescription only medicine<br>**Additional risk minimization measures:**<br>• None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>• None<br>**Additional pharmacovigilance activities:**<br>• None |

| Safety concern | Risk minimization measures | Pharmacovigilance activities |
|---|---|---|
| **Missing information:**<br>**Use in Patients with Prior Intravenous Bisphosphonate Treatment** | **Routine risk minimization measures:**<br>• SmPC: Section 4.5, Section 5.1<br>• PIL: Section 2<br>**Other risk minimization measures**<br>• Legal status: prescription only medicine<br>**Additional risk minimization measures:**<br>• None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>• None<br>**Additional pharmacovigilance activities:**<br>• None |
| **Missing information:**<br>**Safety With Long-Term Treatment and With Long-Term Follow-up After Treatment in Adults and Skeletal Mature Adolescents with GCTB** | **Routine risk minimization measures:**<br>• None<br>**Other risk minimization measures**<br>• Legal status: prescription only medicine<br>**Additional risk minimization measures:**<br>• None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>• None<br>**Additional pharmacovigilance activities:**<br>• None |
| **Missing information:**<br>**Off Label Use in Patients with GCTB That is Resectable Where Resection is Unlikely to Result in Severe Morbidity** | **Routine risk minimization measures:**<br>• None<br>**Other risk minimization measures**<br>• Legal status: prescription only medicine<br>**Additional risk minimization measures:**<br>• None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>• None<br>**Additional pharmacovigilance activities:**<br>• None |

# Part VI: Summary of the Risk Management Plan for Bomyntra (denosumab 120 mg)

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

The Bomyntra'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 Bomyntra 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 Bomyntra RMP.

## I. The medicine and what it is used for

Bomyntra is authorized for prevention of skeletal-related events (pathological fracture, radiation to bone, spinal cord compression, or surgery to bone) in adults with advanced malignancies involving bone and for the treatment of adults and skeletally mature adolescents with giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity (see SmPC for the full indication). It contains denosumab as the active substance and it is given by subcutaneous administration.

Further information about the evaluation of Bomyntra benefits can be found in Bomyntra'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/bomyntra.

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

Important risks of Bomyntra, 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 Periodic Safety Update Report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

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

### *II.A List of important risks and missing information*

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

| **List of important risks and missing information** | |
|---|---|
| Important identified risks | • Osteonecrosis of the Jaw<br>• Atypical Femoral Fracture<br>• Hypercalcemia several months after the last dose in patients with Giant Cell Tumour of Bone and In Patients with Growing Skeletons |
| Important potential risks | • Cardiovascular events<br>• Malignancy<br>• Delay in Diagnosis of Primary Malignancy in Giant Cell Tumour of Bone<br>• Hypercalcemia Several Months After the Last Dose in Patients Other Than Those With Giant Cell Tumour of Bone or Growing Skeletons |
| Missing information | • Use in Patients with Prior Intravenous Bisphosphonate Treatment<br>• Safety With Long-Term Treatment and With Long Term Follow-up After Treatment in Adults and Skeletal Mature Adolescents with GCTB<br>• Off Label Use in Patients with GCTB That is Resectable Where Resection is Unlikely to Result in Severe Morbidity |

## *II.B Summary of important risks*

| **Important identified risk: Osteonecrosis of the Jaw** | |
|---|---|
| Evidence for linking the risk to the medicine | The source of information is clinical/safety and postmarketing data of the reference product Amgen XGEVA (EU-RMP v36.0, 2020) and medical literature. |
| Risk factors and risk groups | Risk factors associated with ONJ include the use of antiresorptive (particularly aminobisphosphonates delivered by intravenous [IV] dosing), older age, poor dental hygiene, periodontal disease, invasive dental procedures, trauma from poorly fitting dentures, malignancy, chemotherapy (including antiangiogenesis agents such as bevacizumab), radiation to head and neck, corticosteroids, hypercoagulable state secondary to underlying malignancy, smoking and vascular insufficiency due to thrombosis (Almazrooa and Woo 2009, Estilo et al. 2008, Mehrotra and Ruggiero 2006, Ruggiero et al. 2006). |
| Risk minimization measures | **Routine risk communication:**<br>SmPC: Section 4.3, Section 4.4, Section 4.8 , Section 5.1<br>PIL: Section 2, Section 4<br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br>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.<br>**Other risk minimization measures beyond the Product Information:**<br>Medicine's legal status: prescription only medicine.<br>**Additional risk minimization measures:**<br>Patient Reminder Card |
| 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 and postmarketing data of the reference product Amgen XGEVA (EU-RMP v36.0, 2020) and medical literature. |

| | |
|---|---|
| Risk factors and risk groups | Long-term anti resorptive 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, rheumatoid arthritis, hypophosphatasia) and with use of bisphosphonates, glucocorticoids, and proton pump inhibitors (Shane et al. 2010). |
| Risk minimization measures | **Routine risk communication:**<br>SmPC: Section 4.4, Section 4.8<br>PIL: Section 2, Section 4<br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br>Recommendation for reporting new or unusual thigh, hip, or groin pain is included Section 4.4 of SmPC.<br>**Other risk minimization measures beyond the Product Information:**<br>Medicine's legal status: prescription only medicine.<br>**Additional risk minimization measures:**<br>None |
| Additional pharmacovigilance activities | None |
| **Important identified risk: Hypercalcemia several months after the last dose in patients with Giant Cell Tumour of Bone and In Patients with Growing Skeletons** | |
| Evidence for linking the risk to the medicine | The source of information is clinical/safety and postmarketing data of the reference product Amgen XGEVA (EU-RMP v36.0, 2020) and medical literature. |
| Risk factors and risk groups | Patients with GCTB and young patients with growing skeletons following discontinuation of XGEVA. In general, the most common cause of hypercalcemia in humans is hyperparathyroidism, particularly among women and individuals aged 65 years or older (Minisola et al. 2015). Hyperthyroidism and rhabdomyolysis associated with renal failure also increase the risk of hypercalcemia, as does the ingestion of large of amounts of calcium through dairy products or more recently liberal use of calcium supplements (Machado et al. 2015, Minisola et al. 2015). |

| | |
|---|---|
| Risk minimization measures | **Routine risk communication:**<br>SmPC: Section 4.4, Section 4.8<br>PIL: Section 2, Section 4<br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br>None<br>**Other risk minimization measures beyond the Product Information:**<br>Medicine's legal status: prescription only medicine.<br>**Additional risk minimization measures:**<br>None |
| Additional pharmacovigilance activities | None |
| **Important potential risk: Cardiovascular events** | |
| Evidence for linking the risk to the medicine | The risk of cardiovascular (CV) events is a safety concern based on the epidemiological association between OPG levels and CV disease in man. Amgen's clinical data have not substantiated a cause-and-effect between OPG and atherosclerotic processes nor between denosumab or inhibition of RANKL and undesirable CV outcomes (Amgen XGEVA EU-RMP v36.0, 2020). |
| Risk factors and risk groups | The Amgen's denosumab development program comprises studies of older subject populations (e.g., osteoporosis, cancer) that are likely to have a higher incidence of pre-existing CV conditions and, thus, a higher incidence of CV toxicities than that of the general population (Hak et al. 2000, Schulz et al. 2004). |
| Risk minimization measures | **Routine risk communication:**<br>Not applicable<br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br>None<br>**Other risk minimization measures beyond the Product Information:**<br>Medicine's legal status: prescription only medicine.<br>**Additional risk minimization measures:**<br>None |

| | |
|---|---|
| Additional pharmacovigilance activities | None |
| **Important potential risk: Malignancy** | |
| Evidence for linking the risk to the medicine | Imbalance is observed in the NPM events between the zoledronic acid and XGEVA treatment groups in Amgen's pivotal clinical studies. The results of an Amgen's postmarketing retrospective cohort study, showed NPM incidence rates for XGEVA were generally lower than those for zoledronic acid in unadjusted analyses, suggesting no obvious excess risk associated with XGEVA (Amgen XGEVA EU-RMP v36.0, 2020). |
| Risk factors and risk groups | General factors for increasing risk of NPM include advancing age, diet, cigarette smoking, excessive ethanol consumption, and numerous environmental toxins. In addition, advanced cancer populations are at increased risk for NPM because of their existing malignancy, possible genetic predisposition, and exposure to chemotherapy and radiation treatment. |
| Risk minimization measures | **Routine risk communication:**<br>SmPC: Section 4.4, Section 4.8, Section 5.1<br>PIL: Section 4<br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br>None<br>**Other risk minimization measures beyond the Product Information:**<br>Medicine's legal status: prescription only medicine.<br>**Additional risk minimization measures:**<br>None |
| Additional pharmacovigilance activities | None |
| **Important potential risk: Delay in Diagnosis of Primary Malignancy in Giant Cell Tumour of Bone** | |
| Evidence for linking the risk to the medicine | The risk of delay in diagnosis of PMGCTB is a regulatory concern based on the difficulties in diagnosing PMGCTB in an Amgen's study (Amgen XGEVA EU-RMP v36.0, 2020). |

| | |
|---|---|
| Risk factors and risk groups | Patients with GCTB are known to be at risk for PMGCTB. |
| Risk minimization measures | **Routine risk communication:**<br>None<br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br>None<br>**Other risk minimization measures beyond the Product Information:**<br>Medicine's legal status: prescription only medicine.<br>**Additional risk minimization measures:**<br>None |
| Additional pharmacovigilance activities | None |
| **Important potential risk: Hypercalcemia Several Months After the Last Dose in Patients Other Than Those With Giant Cell Tumour of Bone or Growing Skeletons** | |
| Evidence for linking the risk to the medicine | Hypercalcemia several months after the last dose in patients other than those with GCTB or growing skeletons is a theoretical concern based on the identified risk in other specific populations, GCTB, and paediatric populations (Amgen XGEVA EU-RMP v36.0, 2020). |
| Risk factors and risk groups | Patients other than those with GCTB or growing skeletons following cessation of denosumab. |
| Risk minimization measures | **Routine risk communication:**<br>None<br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br>None<br>**Other risk minimization measures beyond the Product Information:**<br>Medicine's legal status: prescription only medicine.<br>**Additional risk minimization measures:**<br>None |

| | |
|---|---|
| Additional pharmacovigilance activities | None |
| **Missing information: Use in Patients with Prior Intravenous Bisphosphonate Treatment** | |
| Risk minimization measures | **Routine risk minimization measures:**<br>SmPC: Section 4.5, Section 5.1<br>PIL: Section 2<br>**Additional risk minimization measure:**<br>None |
| Additional pharmacovigilance activities | None |
| **Missing information: Safety With Long-Term Treatment and With Long-Term Follow-up After Treatment in Adults and Skeletal Mature Adolescents with GCTB** | |
| Risk minimization measures | **Routine risk minimization measures:**<br>None<br>**Additional risk minimization measure:**<br>None |
| Additional pharmacovigilance activities | None |
| **Missing information: Off Label Use in Patients with GCTB That is Resectable Where Resection is Unlikely to Result in Severe Morbidity** | |
| Risk minimization measures | **Routine risk minimization measures:**<br>None<br>**Additional risk minimization measure:**<br>None |
| Additional pharmacovigilance activities | 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 Bomyntra.

### 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 |
|---|---|
| Osteonecrosis of the Jaw | 1.0 |
| Postmarketing reports of potential atypical fracture | 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**

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

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

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AER# | Safety database number

Patient identifier | Study number

**Above information to be filled by Fresenius Kabi.**

# 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)

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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: **Osteonecrosis of the Jaw**

## Oral findings

Evidence of infecton:

☐ Yes ☐ No ☐ Unknown

If yes, please describe

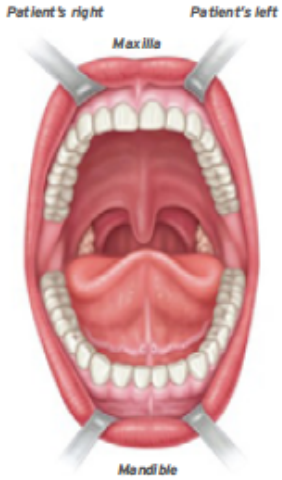
Exposed bone at the site of extraction:

☐ 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

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Patient identifier

Study number

**Above information to be filled by Fresenius Kabi.**

# 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

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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

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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

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# 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:

Global Vigilance
Fresenius Kabi
Borkenberg 14
Oberursel, Deutschland
Email: pharmacovigilance@fresenius-kabi.com
T +49 6172 686 7313
Out-of-office-hours: +49 6172 686 061440
F +49 6172 686 4505

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

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

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

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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

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# 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:

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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:

Global Vigilance
Fresenius Kabi
Borkenberg 14
Oberursel, Deutschland
Email: pharmacovigilance@fresenius-kabi.com
T +49 6172 686 7313
Out-of-office-hours: +49 6172 686 061440
F +49 6172 686 4505

***Annex 6 – Details of proposed additional risk minimisation activities.***

**Key messages of the additional risk minimisation measures**

**Patient Reminder Card**

Patient Reminder Cards for osteonecrosis of the jaw will be distributed to prescribers of Bomyntra 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 (Bomyntra) injections for cancer-related conditions, including:

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