PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for Prolia® (denosumab)

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

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

This summary of the RMP for Prolia® should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Prolia®'s RMP.

I. The medicine and what it is used for

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

Further information about the evaluation of Prolia®'s benefits can be found in Prolia®'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/medicines/human/EPAR/prolia.

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

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

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

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

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

In the case of Prolia® these measures are supplemented with *additional risk minimization measures* mentioned under relevant risks, below.

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

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

II.A. List of Important Risks and Missing Information

Important risks of Prolia® 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 Prolia®. 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 (eg, on the long-term use of the medicine).

List of important risks and missing information	
Important Identified Risk	• Hypocalcemia • Skin infection leading to hospitalisation • Osteonecrosis of the jaw • Hypersensitivity reactions • Atypical femoral fracture • Hypercalcemia in pediatric patients receiving denosumab and after treatment discontinuation
Important Potential Risk	• Fracture healing complications • Infection • Cardiovascular events • Malignancy
Missing Information	• None

II.B. Summary of Important Risks

Important identified risk: Hypocalcemia	
Evidence for linking the risk to the medicine	This risk was identified in the phase 3, randomized, double-blind, placebo- or active-controlled studies.
Risk factors and risk groups	Risk factors include severe renal impairment and hyperphosphatemia. Other risks factors may include a history of hypoparathyroidism, parathyroid hormone resistance, vitamin D deficiency or resistance, thyroid surgery, parathyroid surgery, malabsorption syndromes, excision of small intestine, severe renal impairment (creatinine clearance $<$ 30 mL/min), dialysis, and some medications (Finkelstein, *Cecil Essentials of Medicine, 5th ed*, 2001:639-648).
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4, where recommendation regarding correction and monitoring of calcium levels is provided • SmPC Section 4.2, 4.3, and 4.8 • PL Section 2 and 4 Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Postmarketing observational Study 20090522 • Controlled clinical Study 20130173 See Section II.C of this summary for an overview of the postauthorization development plan

Important identified risk: Skin infection leading to hospitalisation	
Evidence for linking the risk to the medicine	This risk was identified in the phase 3, randomized, double-blind, placebo- or active-controlled studies.
Risk factors and risk groups	Risk factors for infection in general include increasing age, immunosuppression associated with cancer, diabetes, human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), immunosuppressant drugs (eg, corticosteroids, arthritis medications, and chemotherapy drugs), substance abuse, and malnutrition. Risk factors for skin infection in older patients include skin wounds, peripheral vascular disease, eczema/dermatitis, and venous stasis disorders.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4, and 4.8 • PL Section 2 and 4 Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Postmarketing observational Study 20090522 See Section II.C of this summary for an overview of the postauthorization development plan

Important identified risk: Osteonecrosis of the jaw	
Evidence for linking the risk to the medicine	This risk was identified in open-label long-term extensions to phase 3, randomized, double-blind, placebo-controlled studies.
Risk factors and risk groups	Risk factors include duration of exposure to denosumab, prior bisphosphonate use (particularly for extended periods of time), older age, periodontal disease, dentoalveolar surgery, trauma from poorly fitting dentures, malignancy, chemotherapy, corticosteroids, smoking, systemic or regional infection, immune-compromised state predisposing to increased risk of infection, hypercoagulable state secondary to underlying malignancy, and vascular insufficiency due to thrombosis (Mehrotra and Ruggiero, *Hematology*, 2006;356-360; Ruggiero et al, *J Oncol Pract*, 2006;2:7-14).
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4, where oral hygiene and dental management guidance is provided • SmPC Section 4.8 • PL Section 2 and 4 Additional risk minimization measures: • Patient reminder card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Postmarketing observational Study 20090522 See Section II.C of this summary for an overview of the postauthorization development plan

Important identified risk: Hypersensitivity reactions	
Evidence for linking the risk to the medicine	This risk was identified in the postmarketing setting based on a clinically plausible association between administration of denosumab and hypersensitivity events.
Risk factors and risk groups	Known hypersensitivity to denosumab and any of its excipients.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.3 and 4.8 • PL Section 2 and 4 Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Postmarketing observational Study 20090522 See Section II.C of this summary for an overview of the postauthorization development plan

Important identified risk: Atypical Femoral Fracture	
Evidence for linking the risk to the medicine	This risk was identified in an open-label long-term extension to a phase 3, randomized, double-blind, active-controlled study.
Risk factors and risk groups	Long-term antiresorptive treatment has been associated with atypical femoral fracture. Corticosteroids have also been reported in the literature to potentially be associated with atypical femoral fracture (Meier et al, *Arch Intern Med*, 2012;172:930-936; Giusti et al, *Bone*, 2011; 48(5):966-971). Atypical femoral fractures have also been reported in patients with certain comorbid conditions (eg, vitamin D deficiency, rheumatoid arthritis, hypophosphatasia) and with use of bisphosphonates, glucocorticoids, and proton pump inhibitors (Shane et al, *J Bone Miner Res*, 2010;25:2267-2294).
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4, where recommendation for reporting potential symptoms is provided • SmPC Section 4.8 • PL Section 2 and 4 Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Postmarketing observational Study 20090522 • Controlled clinical Study 20130173 See Section II.C of this summary for an overview of the postauthorization development plan

Important identified risk: Hypercalcemia in pediatric patients receiving denosumab and after treatment discontinuation	
Evidence for linking the risk to the medicine	Data to evaluate safety concerns derived from Prolia clinical trials in pediatric subjects with osteogenesis imperfecta, XGEVA clinical studies and postmarketing adverse event reporting involving pediatric patients receiving denosumab at unapproved doses and/or unapproved indications for use.
Risk factors and risk groups	Pediatric patients with growing skeletons and high bone turnover disease states (such as osteogenesis Imperfecta).
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.2 and 4.4 • PL Section 2 Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Controlled clinical Study 20130173 See Section II.C of this summary for an overview of the postauthorization development plan

Important potential risk: Fracture healing complications	
Evidence for linking the risk to the medicine	This is a theoretical risk based on the potential mechanism of action.
Risk factors and risk groups	General risk factors for fracture healing complications are thought to include older age, diabetes, use of medications such as non-steroidal anti-inflammatory drugs and corticosteroids, smoking, excessive alcohol use, and poor nutrition (Hernandez et al, *Acta Orthopaedica*, 2012;83(6):653-660; Gaston and Simpson, *J Bone Joint Surg [Br]*, 2007;89-B:1553-1560).
Risk minimization measures	Routine risk minimization measures: • SmPC Section 5.3 Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Postmarketing observational Study 20090522 See Section II.C of this summary for an overview of the postauthorization development plan

Important potential risk: Infection	
Evidence for linking the risk to the medicine	This is considered a potential risk based on theoretical concerns which has not been substantiated in the extensive clinical study program or in the postmarketing experience.
Risk factors and risk groups	Risk factors for infection in general include increasing age, immunosuppression associated with cancer, diabetes, HIV/AIDS, immunosuppressant drugs (eg, corticosteroids, arthritis medications, and chemotherapy drugs), substance abuse, and malnutrition.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.8 • PL Section 4 Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Postmarketing observational Study 20090522 See Section II.C of this summary for an overview of the postauthorization development plan

Important potential risk: Cardiovascular events	
Evidence for linking the risk to the medicine	This is a theoretical risk based on epidemiological data demonstrating elevated osteoprotegerin in patients with cardiovascular disease.
Risk factors and risk groups	The denosumab development program comprises studies of older subject populations (eg, osteoporosis, cancer) that are likely to have a higher incidence of pre-existing cardiovascular conditions and, thus, a higher incidence of cardiovascular toxicities than that of the general population (Schulz et al, *J Clin Endocrinol Metab*, 2004;89:4246-4253; Hak et al, *Arterioscler Thromb Vasc Biol*, 2000;20:1926-1931). Risk factors for atherosclerosis include age, sex, ethnicity, family history, elevated lipid levels, cigarette smoking, hypertension, diabetes, and concomitant medications, including antipsychotic agents and COX-2 inhibitors (Murphy and Dargie, *Drug Safety*, 2007;30(9):783-804; Smith et al, *Circulation*, 2004;109(21):2613-2616).
Risk minimization measures	Routine risk minimization measures: • None Additional risk minimization measures: • None

Important potential risk: Malignancy	
Evidence for linking the risk to the medicine	This is considered a potential risk based on theoretical concerns and has not been substantiated in the extensive clinical study program or in the postmarketing experience.
Risk factors and risk groups	General factors for risk of malignancy include advancing age, diet, cigarette smoking, excessive ethanol consumption, and numerous environmental toxins. In addition, cancer populations are at increased risk for a second primary malignancy because of their existing malignancy, possible genetic predisposition, and exposure to chemotherapy and radiation treatment (Anand et al, *Pharm Res*. 2008; 25(9):209-72116; World Health Organization, Global Status Report on Noncommunicable Diseases 2010, http://www.who.int).
Risk minimization measures	Routine risk minimization measures: • None Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Postmarketing observational Study 20090522 See Section II.C of this summary for an overview of the postauthorization development plan

II.C. Postauthorization Development Plan

II.C.1. Studies Which Are Conditions of the Marketing Authorization

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

II.C.2 Other Studies in Postauthorization Development Plan

Study Short Name	Purpose of the Study
20090522 Postmarketing observational study Denosumab global safety assessment among women with postmenopausal osteoporosis (PMO), men with osteoporosis, and men and women who receive Prolia with glucocorticoid exposure in multiple observational databases.	Rationale: A favorable benefit-risk profile of denosumab 60 mg every 6 months (Prolia®) for the treatment of PMO and bone loss associated with hormone ablation in men with prostate cancer was characterized in the original marketing application, which was approved by EMA on 26 May 2010. Amgen also committed to conduct a long-term observational study in administrative databases to prospectively evaluate the incidence of adverse events of special interest (AESI) in postmenopausal women administered Prolia (denosumab). Additional target populations have been added for use of denosumab in men with osteoporosis, and in men and women who receive Prolia with glucocorticoid-induced osteoporosis. Objectives: • Determine incidence of AESI in women with PMO exposed to denosumab, women with PMO exposed to bisphosphonates, and among all women with PMO • Describe characteristics, clinical features, and AESI risk factors in women with PMO exposed to denosumab, women with PMO exposed to bisphosphonates, and all women with PMO • Compare the incidence of the AESI in women with PMO exposed to denosumab to that in women with PMO exposed to bisphosphonates • Describe incidence of AESI in postmenopausal women • Describe denosumab utilization patterns in subjects who receive denosumab therapy for treatment of PMO • Describe Prolia utilization patterns in subjects who receive Prolia therapy for unapproved indications (indication, dosage, frequency) • In men with osteoporosis treated with denosumab, describe subject characteristics, clinical features, AESI risk factors, subject follow-up, incidences of AESI, and denosumab utilization patterns (United States Medicare data system and United Healthcare data system)

Study Short Name	Purpose of the Study
20090522 (Continued)	• In men and women who receive Prolia with glucocorticoid exposure, describe subject characteristics, clinical features, AESI risk factors, subject follow-up, incidences of AESI, and denosumab utilization patterns (US Medicare data system and Optum Research database [previously called United Healthcare]) Safety concerns addressed: Hypocalcemia, osteonecrosis of the jaw, atypical femoral fracture, fracture healing complications, infection, hypersensitivity reactions, malignancy.
20130173 Controlled clinical study Prospective, multicenter, single-arm study to evaluate efficacy, safety, and pharmacokinetics of denosumab in children with osteogenesis imperfecta	Rationale: This study is part of a Paediatric Investigation Plan (PIP) for denosumab (Prolia) that was agreed upon with the EMA. Objectives: Evaluate the effect of denosumab on lumbar spine bone marrow density Z-score at 12 months, as assessed by dual-energy X-ray absorptiometry (DXA), in children 2 to 17 years of age with osteogenesis imperfecta. Safety concerns addressed: Hypocalcemia, atypical femoral fracture, hypercalcemia in pediatric patients receiving denosumab and after treatment discontinuation