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Swiss Summary of the Risk Management Plan (RMP) for XGVEA® (denosumab)

EU RMP: Version 37.1, 19 September 2025

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of XGEVA® is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the “Arzneimittelinformation / Information sur le médicament” approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of XGEVA® in Switzerland is the “Arzneimittelinformation / Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic. AMGEN Switzerland AG is fully responsible for the accuracy and correctness of the content of the published RMP summary of XGEVA®.

The medicine and what it is used for

XGEVA 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 tumor 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 XGEVA's benefits can be found in XGEVA's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: <https://www.ema.europa.eu/en/medicines/human/EPAR/XGEVA>.

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

Important risks of XGEVA, together with measures to minimize such risks and the proposed studies for learning more about XGEVA'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 XGEVA, these measures are supplemented with *additional risk minimization measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly 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 XGEVA is not yet available, it is listed under 'missing information' below.

List of Important Risks and Missing Information

Important risks of XGEVA 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 XGEVA. 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).

Summary of safety concerns

List of important risks and missing information	
Important identified risks	- Osteonecrosis of the jaw - Atypical femoral fracture
Important potential risks	- Cardiovascular events - Hypercalcemia several months after the last dose in patients other than those with giant cell tumor of bone or growing skeletons
Missing information	- Patients with prior intravenous bisphosphonate treatment - Off-label use in patients with giant cell tumor of bone that is resectable where resection is unlikely to result in severe morbidity

Summary of Important Risks

Important identified risk: Osteonecrosis of the Jaw	
Evidence for linking the risk to the medicine	This risk was identified in randomized, controlled, phase 3 clinical trials. This risk was further supported by postmarketing reports.
Risk factors and risk groups	Risk factors associated with osteonecrosis of the jaw (ONJ) include the use of antiresorptives (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 minimization measures: • SmPC Section 4.3 • SmPC Section 4.4 • SmPC Section 4.8 • SmPC Section 5.1 • Package Leaflet (PL) Section 2 • PL Section 4 Additional risk minimization measures: • Patient reminder cards

Important identified risk: Atypical Femoral Fracture	
Evidence for linking the risk to the medicine	This risk was identified in randomized, controlled, phase 3 clinical trials and in open-label, phase 2 clinical trials. This risk was further supported by postmarketing reports.
Risk factors and risk groups	Long-term antiresorptive treatment has been associated with atypical femoral fracture (AFF). Corticosteroids have also been reported in the literature to potentially be associated with AFF (Meier et al, 2012; Giusti et al, 2011). Atypical femoral fractures have also been reported in patients with certain comorbid conditions (eg, vitamin D deficiency, rheumatoid arthritis [RA], hypophosphatasia) and with use of bisphosphonates, glucocorticoids, and proton pump inhibitors (Shane et al, 2010).
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 Additional risk minimization measures: • None

Important potential risk: Cardiovascular Events	
Evidence for linking the risk to the medicine	The risk of cardiovascular events is a regulatory concern based on the epidemiological association between osteoprotegerin (OPG) levels and cardiovascular disease in man. Clinical data have not substantiated a cause-and-effect between OPG and atherosclerotic processes nor between denosumab or inhibition of receptor activator of nuclear factor kappa B-ligand (RANKL) and undesirable cardiovascular outcomes.
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, 2004; Hak et al, 2000). 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).
Risk minimization measures	Routine risk minimization measures: • None Additional risk minimization measures: • None

Important potential risk: Hypercalcemia Several Months After the Last Dose in Patients Other Than Those With Giant Cell Tumor 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 pediatric populations.
Risk factors and risk groups	Patients other than those with GCTB or growing skeletons following cessation of XGEVA.
Risk minimization measures	Routine risk minimization measures: • None Additional risk minimization measures: • None

Missing Information: Patients With Previous Intravenous Treatment With Bisphosphonate Treatment	
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.5 • SmPC Section 5.1 • PL Section 2 Additional risk minimization measures: • None

Missing Information: Off label use in patients with giant cell tumor of bone that is resectable where resection is unlikely to result in severe morbidity	
Risk minimization measures	Routine risk minimization measures: • None Additional risk minimization measures: • None

Post-authorization development plan

- Studies Which Are Conditions of the Marketing Authorization

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

- Other Studies in Postauthorization Development Plan

There are no studies required for XGEVA.

This summary was last updated in October 2026.