

Part VI: Summary of the risk management plan

Summary of risk management plan for NERIXIA (Sodium neridronate)

This is a summary of the risk management plan (RMP) for NERIXIA 25 mg solution for injection and 100 mg concentrate for solution for infusion.

The RMP details important risks of NERIXIA, how these risks can be minimised, and how more information will be obtained about NERIXIA's risks and uncertainties (missing information).

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

I. The medicine and what it is used for

NERIXIA is authorised for Osteogenesis imperfecta, Paget's disease and Algodystrophy (e.v. and i.m.). See SmPc for the full indication.

It contains sodium neridronate as the active substance and it is given by slow intravenous infusion or by intramuscular administration.

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

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

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

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

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

There are not additional risk minimisation measures mentioned under relevant important risks.

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

II.A List of important risks and missing information

Important risks of NERIXIA are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of NERIXIA. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	Osteonecrosis of the jaw Atypical femoral fractures
Important potential risks	None
Missing information	None

II.B Summary of important risks

Important identified risk: Osteonecrosis of the jaw	
Evidence for linking the risk to the medicine	<p>The first reports describing osteonecrosis of the jaw (ONJ) in patients receiving bisphosphonates were published in 2003. High-dose intravenous bisphosphonates have been identified as a risk factor for ONJ among oncologic patients. Low dose bisphosphonate use in patients with osteoporosis or other metabolic bone disease has not been causally linked to the development of ONJ.</p> <p>About 95% of the reported cases occurred among cancer patients receiving high-dose intravenous bisphosphonates. Approximately 5% of the reported cases have been in osteoporosis patients receiving low-dose bisphosphonate therapy.</p> <p>Since first authorization, respectively, only five (5) cases of ONJ and three (3) cases for osteonecrosis were collected for the medicinal products NERIXIA/neridronate.</p>

Risk factors and risk groups	<p>ONJ is dependent on dose and duration of therapy; exposure to intravenous bisphosphonates for the management of malignancy remains the sole main risk factor for the development of ONJ, as the prevalence in such patients ranges from 0.8 to 12%.</p> <p>The factors to develop this condition may be divided into three: risk factors related to drug intake, local risk factors, and systemic risk factors. The American Association of Oral and Maxillofacial Surgeons (AAOMS), in 2009, also mentioned anatomic traits (torus palatinus and mandibular, the mylohyoid line), advanced age, being of Caucasian descent, and other genetic specificities as additional risk factors. However, the long-term use of bisphosphonates is thought to be the main risk factor for atypical femoral fractures. Despite being low, the risk of developing ONJ increases when bisphosphonates use is longer than three years, and such time is reduced for patients on chronic corticosteroids.</p>
Risk minimisation measures	<p><u>Routine risk minimisation measures:</u></p> <p>Information in PL sections 2.</p> <p>NERIXIA medicinal products are prescription medicines.</p> <p><u>Additional risk minimisation measures:</u></p> <p>No risk minimisation measures.</p>
Additional pharmacovigilance activities	None

Important identified risk: Atypical femoral fractures	
Evidence for linking the risk to the medicine	CHMP scientific conclusion regarding the Article 20 and Article 31 Referrals on bisphosphonates and atypical femoral fractures which considered pre-clinical, clinical, epidemiological studies, post-marketing reports and published literature.
Risk factors and risk groups	A number of possible risk factors have been

	<p>proposed for atypical femoral fractures in association with bisphosphonate use. The long-term use of bisphosphonates is thought to be the main risk factor for atypical femoral fractures. However, the optimal duration of use of bisphosphonates for osteoporosis is not known. There is currently no robust evidence regarding the value of interrupting treatment with bisphosphonates. Glucocorticoids and proton pumps inhibitor (PPI) have been identified as possible important risk factors for atypical femur fracture. Concomitant treatment with other anti-resorptive drugs such as hormone replacement therapy and raloxifene have also been proposed as possible risk factors. Other than osteoporosis the most prevalent co-morbid conditions in patients with atypical femur fracture were found to be chronic obstructive pulmonary disease or asthma, rheumatoid arthritis and diabetes.</p>
Risk minimisation measures	<p><u>Routine risk minimisation measures:</u></p> <p>Information in SmPC sections 4.4 and 4.8. Information in PL section 4.</p> <p>NERIXIA medicinal products are prescription medicines.</p> <p><u>Additional risk minimisation measures:</u> No risk minimisation measures.</p>
Additional pharmacovigilance activities	None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of NERIXIA.

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

There are no studies required for NERIXIA.