SANDOZ

Patient Safety & Pharmacovigilance

Pegfilgrastim
6 mg/0.6 ml
Solution for injection in prefilled syringes

LA-EP2006

Summary of the EU Safety Risk Management Plan
Sandoz Pharmaceuticals AG, Rotkreuz, CH

Active substance(s) (INN or common name):	Pegfilgrastim
Product(s) concerned (brand name(s)):	Ziextenzo
Document status:	Final
Version number of the RMP Public Summary:	2.0
Date of final sign off of the RMP Public Summary:	28-Nov-2022
Number of pages	8

Sandoz template version 1.0, dated 20-May-2019

Disclaimer:

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 Ziextenzo 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 Ziextenzo in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Sandoz Pharmaceuticals AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Ziextenzo.

Summary of the risk management plan Ziextenzo (pegfilgrastim)

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

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

This summary of the RMP for Ziextenzo 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 Ziextenzo's RMP.

I. The medicine and what it is used for

Ziextenzo is used to increase the number of white blood cells after treatment with chemotherapy to help to prevent the risk of infections. It contains pegfilgrastim as the active substance and it is given by subcutaneous injection.

White blood cells are very sensitive to the effects of chemotherapy which can lower the number of these cells in the body.

White blood cells are important as they help the body to fight infection. If the number of white blood cells fall to a low level (so-called neutropenia), there may not be enough left in the body to fight bacteria and the risk of infection may be increased.

Patients with a low number of white blood cells who develop fever may be at risk of infection of the whole body (also called 'sepsis'). Sepsis is a serious condition that requires urgent diagnosis and treatment.

Further information about the evaluation of Ziextenzo's benefits can be found in Ziextenzo's EPAR, including in its plain-language summary, available on the EMA website: https://www.ema.europa.eu/en/medicines/human/EPAR/ziextenzo.

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

Important risks of Ziextenzo's together with measures to minimize such risks and the proposed studies for learning more about Ziextenzo'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 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 minimize its risks.

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

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

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

II.A: List of important risks and missing information

Important risks of Ziextenzo 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 Ziextenzo. 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

List of important risks and missing information	
Important identified risks	Capillary leak syndrome Acute respiratory distress syndrome Sickle cell crisis in patients with sickle cell disease Glomerulonephritis
Important potential risks	Cytokine release syndrome
Missing information	None

II.B: Summary of important risks

Important identified risk: Capillary leak syndrome

Evidence for linking the risk to the medicine	Capillary leek syndrome is listed in section 4.4 Special warnings and precautions and section 4.8 Undesirable effects of the Neulasta SmPC and is therefore considered as an important identified risk of LA-EP2006.
Risk factors and risk groups	Multiple drug therapy, cancer patients receiving chemotherapy, middle age

Risk minimization measures	Routine risk minimization measures: SmPC sections 4.4 and 4.8 Routine risk minimization activities recommending specific clinical measures to address the risk Close monitoring of patients who develop symptoms of capillary leak syndrome and receive standard symptomatic treatment, which may include a need for intensive care Legal status: prescription only Additional risk minimization measures: None

Important identified risk: Acute respiratory distress syndrome

Evidence for linking the risk to the medicine	Acute respiratory distress syndrome is described under 'Pulmonary adverse events' in section 4.4 Special warnings and precautions and is listed in section 4.8 Undesirable effects of the Neulasta SmPC and are therefore considered as an important identified risk of LA-EP2006.
Risk factors and risk groups	Acute respiratory distress syndrome may occur in people of any age. Acute respiratory distress syndrome incidence increases with advancing age, ranging from 16 cases per 100,000 person-years in those aged 15-19 years to 306 cases per 100,000 person-years in those between the ages of 75 and 84 years. The age distribution reflects the incidence of the underlying causes.
Risk minimization measures	Routine risk minimization measures SmPC sections 4.4 and 4.8 Routine risk minimization activities recommending specific clinical measures to address the risk Deterioration in pulmonary function along with increased neutrophil count may be preliminary signs of ARDS. Legal status: prescription only Additional risk minimization measures: None

Important identified risk: Sickle cell crisis in patients with sickle cell disease

Evidence for linking the risk to the medicine	Sickle cell crisis in patients with sickle cell disease is listed in section 4.4 Special warnings and precautions and section 4.8 Undesirable effects of the Neulasta SmPC and is therefore considered as an important identified risk of LA-EP2006.
Risk factors and risk groups	Approximately half the individuals with homozygous HbS disease experience vaso-occlusive crisis. Often, no precipitating cause can be identified. However, because deoxygenated HbS becomes semisolid, the most likely physiologic trigger of vaso-occlusive crises is hypoxemia. This may be due to acute chest syndrome or accompany respiratory complications. Dehydration can precipitate pain, since acidosis results in a shift of the oxygen dissociation curve (Bohr effect), causing hemoglobin to de-saturate more readily. Hemo-concentration also is a common mechanism. Another common trigger is changes in body temperature—whether an increase due to fever or a decrease due to environmental temperature change. Lowered body temperature likely leads to crises as the result of peripheral vasoconstriction. Patients should wear proper clothing and avoid exposure to ensure normal core temperature.
Risk minimization measures	Routine risk minimization measures SmPC sections 4.4 and 4.8 Routine risk minimization activities recommending specific clinical measures to address the risk Recommendation to monitor the appropriate clinical parameters Legal status: prescription only Additional risk minimization measures: None

Important identified risk: Glomerulonephritis

Evidence for linking the risk to the medicine	Glomerulonephritis is listed in section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects of the Neulasta SmPC and is therefore considered as an important identified risk of LA-EP2006.
Risk factors and risk groups	Risk factors or risk groups could not be identified.

Risk minimization measures	Routine risk minimization measures SmPC sections 4.4 and 4.8 Routine risk minimization activities recommending specific clinical measures to address the risk Recommendation to monitor urine Legal status: prescription only Additional risk minimization measures: None

Important potential risk: Cytokine release syndrome

Evidence for linking the risk to the medicine	No events of cytokine release syndrome of cytokine storm were reported in clinical studies. No non-study reports of cytokine release syndrome or cytokine storm were consistent with the clinical definition of cytokine release syndrome. Cytokine release syndrome is included as a potential risk per the recommendation from the PRAC (EMA/PRAC/693228/2013, EMA/PRAC/720475/2013/Rev. 1), after consideration of the available evidence from case reports in EudraVigilance and the scientific literature.
Risk factors and risk groups	The administration of monoclonal antibodies and other drugs elicit infusion reactions, and the risk factors for cytokine release syndrome-mediated infusion reactions remain unclear. The severity of the infusion reaction might be related to the number of circulating lymphocytes. During the first infusion of rituximab to patients with relapsed B-cell chronic lymphocytic leukemia or low- grade B-cell Iymphoma, patients with lymphocyte counts >50 x 10^9/L were significantly more likely to have severe symptoms than those having lower baseline lymphocyte counts (p=0.0017). A person's risk for an infusion reaction to a monoclonal antibody is influenced by the route and rate of administration, drug form, whether the drug is given in combination or as a single agent, and concomitant medications. Geographic location may elevate the risk for an infusion reaction from cetuximab.
Risk minimization measures	Routine risk minimization measures Cytokine release syndrome is a disorder characterized by nausea, headache, hypotension, shortness of breath and rash caused by release of cytokines from the cells. All single symptoms are addressed under the respective symptoms. Legal status: prescription only

Additional risk minimization measures: None

II.C: Post-authorization 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 Ziextenzo.

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

There are no studies required for Ziextenzo.