SANDOZ A Novartis Division

Regulatory Affairs Biopharmaceuticals

LA-EP2006 (INN: pegfilgrastim)
6 mg/0.6 mL
Solution for Injection

722-0516-rmp-summary-100-1-0

Ziextenzo (Pegfilgrastim)
RMP summary based on RMP version 1.2
Sandoz Pharmaceuticals AG

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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.

Part VI: Summary of the risk management plan for Ziextenzo (pegfilgrastim)

This is a summary of the risk management plan (RMP) for Ziextenzo. 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 http://www.ema.europa.eu/ema/index.jsp?curl=/pages/medicines/human/medicines/004802/human_med_002327.jsp&mid=WC0b01ac058001d124.

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).

Table 1 List of important risks and missing information

List of important risks and missing information	
Important identified risks	Splenomegaly/splenic rupture
	Cutaneous vasculitis
	Sweet's syndrome (acute febrile neutrophilic dermatosis)
	Hypersensitivity (hypersensitivity, anaphylactic reaction, anaphylactoid reaction)
	Capillary leak syndrome
	Serious pulmonary adverse events (including interstitial pneumonia and ARDS)
	Sickle cell crisis in patients with sickle cell disease
	Musculoskeletal pain-related symptoms
	Leukocytosis
	Thrombocytopenia
	Glomerulonephritis
Important potential risks	Acute myeloid leukemia/myelodysplastic syndrome (AML/MDS)
	Cytokine release syndrome
	Medication errors including overdose
	Drug interaction with lithium
	Off-label use
	Immunogenicity (incidence and clinical implications of anti-pegfilgrastim antibodies)
	Extramedullary hematopoiesis (EMH)
Missing information	Risks in children <18 years of age
	Risks during pregnancy and lactation

II B: Summary of important risks

Table 2 Important identified risk: Splenomegaly/splenic rupture

Evidence for linking the risk to the medicine	Splenomegaly and splenic rupture are listed in section 4.4 Special warnings and precautions and 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	Age and race are no risk factors, although patients with sickle cell anaemia have an increased risk. Generally, hematological and systemic autoimmune diseases and infections with mastocytes are risk factors.
Risk minimization measures	Routine risk minimization measures SmPC sections 4.4, 4.8 and 5.3 Additional risk minimization measures: Spleen size should be carefully monitored (e.g. clinical examination, ultrasound). A diagnosis of splenic rupture should be considered in patients reporting left upper abdominal pain or shoulder tip pain.

Table 3 Important identified risk: Cutaneous vasculitis

Evidence for linking the risk to the medicine	Cutaneous vasculitis is listed in 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	Cutaneous vasculitis may be secondary to medications, underlying infection, collagen-vascular disorders, or malignancy. However, approximately half of cases are idiopathic.
Risk minimization measures	Routine risk minimization measures SmPC section 4.8 Additional risk minimization measures: None

Table 4 Important identified risk: Sweet's syndrome (acute febrile neutrophilic dermatosis)

Evidence for linking the risk to the medicine	Sweet's syndrome is listed in 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	There is a female predominance, with a female-to-male ratio of 15:1. However, this predilection was not noted in series of cases associated with malignancy.
Risk minimization measures	Routine risk minimization measures SmPC section 4.8 Additional risk minimization measures: None

Table 5 Important identified risk: Hypersensitivity, including anaphylactic reactions

Evidence for linking the risk to the medicine	Hypersensitivity, including anaphylactic reactions, 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	Drug allergy typically occurs in young and middle-aged adults, and is more common in women than men. Genetic polymorphisms in the human leukocyte antigen (HLA; a gene product of the major histocompatibility complex) as well as viral infections such as HIV and the Epstein-Barr virus (EBV) have also been linked to an increased risk of developing immunologic reactions to drugs. Susceptibility to drug allergy is influenced by genetic polymorphisms in drug metabolism. In addition, topical, intramuscular, and intravenous routes of administration are more likely to cause allergic drug reactions than oral administration; while intravenous administration is associated with more severe reactions. Prolonged high doses or frequent doses are more likely to lead to hypersensitivity reactions than a large single dose. Furthermore, large macromolecular drugs (e.g. insulin or horse antisera) or drugs that haptenate (bind to tissue or blood proteins and elicit an immune response), such as penicillin, are also associated with a greater likelihood of causing hypersensitivity reactions.
Risk minimization measures	Routine risk minimization measures SmPC sections 4.3, 4.4, 4.8 and 6.6 Additional risk minimization measures: Permanently discontinue pegfilgrastim in patients with clinically significant hypersensitivity. Do not administer pegfilgrastim to patients with a history of hypersensitivity to pegfilgrastim or filgrastim. If a serious allergic reaction occurs, appropriate therapy should be administered, with close patient follow-up over several days.

Table 6 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 Additional risk minimization measures: Close monitoring of patients who develop symptoms of capillary leak syndrome and receive standard symptomatic treatment, which may include a need for intensive care

Table 7 Important identified risk: Serious pulmonary adverse events (including interstitial pneumonia and ARDS)

Evidence for linking the risk to the medicine	Serious pulmonary adverse events (including interstitial pneumonia and ARDS) are listed in section 4.4 Special warnings and precautions and 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	Interstitial pneumonia and ARDS may occur in people of any age. ARDS 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 Additional risk minimization measures: Deterioration in pulmonary function along with increased neutrophil count may be preliminary signs of ARDS

Table 8 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 Additional risk minimization measures: Clinicians should monitor appropriate clinical parameters and laboratory status and be attentive to the possible association of this medicine with splenic enlargement and vaso-occlusive crisis.

Table 9 Important identified risk: Musculoskeletal pain-related symptoms

Evidence for linking the risk to the medicine	Musculoskeletal pain-related symptoms (musculoskeletal pain, musculoskeletal chest pain, bone pain) are 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	No specific risk factors are known.
Risk minimization measures	Routine risk minimization measures SmPC section 4.8 Additional risk minimization measures: None

Table 10 Important identified risk: Leukocytosis

Evidence for linking the risk to the medicine	Leukocytosis 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	No risk groups or risk factors are known.
Risk minimization measures	Routine risk minimization measures SmPC sections 4.4 and 4.8 Additional risk minimization measures: Recommendation to monitor the WBC

Table 11 Important identified risk: Thrombocytopenia

Evidence for linking the risk to the medicine	Thrombocytopenia 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	Cancer patients, in particular those treated with cytotoxic chemotherapy.
Risk minimization measures	Routine risk minimization measures SmPC sections 4.4 and 4.8 Additional risk minimization measures: None

Table 12 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 Additional risk minimization measures: Generally, events of glomerulonephritis resolved after dose reduction or withdrawal of filgrastim and pegfilgrastim. Recommendation of urinalysis monitoring.

Table 13 Important potential risk: Acute myeloid leukemia/Myelodysplastic syndrome (AML/MDS)

Evidence for linking the risk to the medicine	As per Neulasta SmPC, the safety and efficacy of Neulasta have not been investigated in patients with myelodysplastic syndrome, chronic myelogenous leukemia, and in patients with secondary AML; therefore, it should not be used in such patients. A published meta-analysis found that in studies with G-CSF delivered chemotherapy dose-intensity and risk of AML/MDS were increased but all-cause mortality was decreased in patients receiving chemotherapy with G-CSF support. The frequency of AML/ADS was increased by 0.4% by added G-CSF in comparison to chemotherapy alone.
Risk factors and risk groups	Known groups with elevated risk are relatives of leukemia patients.

	Known risk factors include chemotherapy, radiation and other environmental factors (chemicals, radiation, etc.)
Risk minimization measures	Routine risk minimization measures SmPC section 4.4 Additional risk minimization measures: None

Table 14 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 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 lymphoma, 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. Additional risk minimization measures: None

Table 15 Important potential risk: Medication errors including overdose

Evidence for linking the risk to the medicine	Three cases of pegfilgrastim overdose have been published. Outcomes were uneventful or controllable. It is assumed that medication errors or overdose with pegfilgrastim are very rare.
Risk factors and risk groups	Patients treated with pegfilgrastim
Risk minimization measures	Routine risk minimization measures SmPC sections 4.9 and 5.3 Additional risk minimization measures: None

Table 16 Important potential risk: Drug interaction with lithium

Evidence for linking the risk to the medicine	The potential for interaction with lithium, which also promotes the release of neutrophils, has not been specifically investigated. There is no evidence that such an interaction would be harmful.

Risk factors and risk groups	Patients under lithium therapy
Risk minimization measures	Routine risk minimization measures SmPC section 4.5 Additional risk minimization measures: None

Table 17 Important potential risk: Off-label use

Evidence for linking the risk to the medicine	As LA-EP2006 is not marketed yet, no off-label use has been observed. The following information was derived from the EPAR of Ristempa: It is known that pegfilgrastim has been used off-label to treat AML, MDS, peripheral blood stem cell apheresis/harvest, idiopathic neutropenia/agranulocytosis, and unspecified leukemia. Information on how well Ristempa works in other conditions or what side effects could be seen is not available.
Risk factors and risk groups	Not applicable
Risk minimization measures	Routine risk minimization measures Off-label use is an inherent risk of all registered medicines. SmPC section 4.2.Additional risk minimization measures: None

Table 18 Important potential risk: Immunogenicity (incidence and clinical implications of anti-pegfilgrastim antibodies)

Evidence for linking the risk to the medicine	As per Neulasta SmPC, as with all therapeutic proteins, there is a potential for immunogenicity. Rates of generation of antibodies against pegfilgrastim are generally low. Binding antibodies do occur as expected with all biologics; however, they have not been associated with neutralising activity at present.
Risk factors and risk groups	Not known
Risk minimization measures	Routine risk minimization measures SmPC section 4.4 Additional risk minimization measures: None

Table 19 Important potential risk: Extramedullary hematopoiesis (EMH)

Evidence for linking the risk to the medicine	A review of a potential signal of EMH retrieved a total of 26 cases for filgrastim and 2 cases for pegfilgrastim. In filgrastim cases, the most common site manifestation was the spleen. Both pegfilgrastim cases involved the spleen. All of the adverse events had alternative explanations and there was no evidence to justify an association between G-CSF and EMH-related symptoms in organs other than the spleen.
Risk factors and risk groups	EMH is a complication of chronic haematological disorder such myeloproliferative disorders, chronic myelogenous leukemia, polycythemia vera, essential thrombocytosis, myelofibrosis with myeloid metaplasia, haemoglobinopathies, sickle cell disease, and thalassemia.

Risk minimization measures	Routine risk minimization measures Currently available data do not support the need of risk minimization. Splenic enlargement (splenomegaly) and splenic rupture in SmPC sections 4.4, 4.8 and 5.3 Additional risk minimization measures: None

Table 20 Missing information: Risks in children <18 years of age

Risk minimization measures	Routine risk minimization measures SmPC sections 4.2, 4.8, 5.1 and 5.2 Additional risk minimization measures: None

Table 21 Missing information: Risks during pregnancy and lactation

Risk minimization measures	Routine risk minimization measures SmPC sections 4.6 and 5.3 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.