European Union Risk Management Plan for Ziextenzo (Pegfilgrastim) (LA-EP2006)

RMP version to be assessed as part of this application	
RMP version number	3.0
Data lock point for this RMP	31 Dec 2025
Date of final sign off	04 Mar 2026
Rationale for submitting an updated RMP	This Risk Management Plan (RMP) has been updated to align with the reference product Neulasta's® (pegfilgrastim) RMP v11.0 dated 20 May 2025, (Amgen Europe B.V.), available on the European Medicines Agency (EMA) website, (last updated on 08 Dec 2025).

Summary of Significant Changes in This RMP Version

RMP part/module	High level description of major changes
Part I Product overview	Pharmacotherapeutic group, brief description of the product, dosage in the European Economic Area (EEA) and pharmaceutical form and strength have been updated.
Part II - Module SVII and Module SVIII	These sections have been revised with updates to the safety concerns in order to align with the reference product Neulasta's (pegfilgrastim) RMP v11.0 dated 20 May 2025.
Part VI Summary of the risk management plan	This section has been revised to align with Part 1 and Part II module SVIII.
Part VII Annexes	Annex 4: TFUQs have been updated to allign with reference product Neulasta's (pegfilgrastim) RMP v11.0 dated 20 May 2025. Annex 7: Updated reference details. Annex 8: Summary of changes to the risk management plan over time has been updated.
Other	RMP has been revised to present the data according to the Good Pharmacovigilance Practices Module V Revision 2 requirements The logo (Sandoz (A Novartis Division) to Sandoz) and template have been updated following the completion of Sandoz's spinoff from Novartis..

Other RMP versions under evaluation: No RMP versions are currently under evaluation.

Details of the currently approved RMP	
Version number	2.0
Approved with procedures	EMEA/H/C/004802/R/0025
Date of approval (opinion date)	26 Apr 2023

QPPV Details	
QPPV name:	Dr. Mohamed Ali Kotal
QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV/deputy.
QPPV/deputy signature:	I am approving this document as Deputy QPPV on behalf of the EU QPPV.

Table of contents

Table of contents 3
List of tables 5
List of abbreviations 6
Part I: Product(s) Overview 7
Part II Safety specification 9
Part II: Module SI - Epidemiology of the indication(s) and target population(s) 9
Part II: Module SII - Non-clinical part of the safety specification 10
Part II: Module SIII - Clinical trial exposure 11
Part II: Module SIV - Populations not studied in clinical trials 15
Module SIV.1. Exclusion criteria in pivotal clinical studies within the development program 15
Module SIV.2. Limitations to detect adverse reactions in clinical trial development programs 19
Module SIV.3. Limitations in respect to populations typically underrepresented in clinical trial development programs 22
Part II: Module - SV: Post-authorization experience 24
SV.1. Post-authorization exposure 24
SV.1.1 Method used to calculate exposure 24
SV.1.2. Exposure 24
Part II: Module - SVI: Additional EU requirements for the safety specification 25
Part II: Module SVII - Identified and potential risks 26
Part II SVII.1. Identification of safety concerns in the initial RMP submission 26
Part II SVII.2: New safety concerns and reclassification with a submission of an updated RMP 26
Part II SVII.3: Details of important identified risks, important potential risks, and missing information 26
SVII.3.1. Presentation of important identified risks and important potential risks 26
SVII.3.2. Presentation of the missing information 31
Part II: Module SVIII - Summary of the safety concerns 32
Part III: Pharmacovigilance plan (including post-authorization safety studies) 33
Part III.1. Routine pharmacovigilance activities 33
Part III.2. Additional pharmacovigilance activities 33

Part III.3. Summary Table of additional pharmacovigilance activities 33
Part IV: Plans for post-authorization efficacy studies 34
Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities) 35
Part V.1. Routine risk minimization measures 35
Part V.2. Additional Risk minimization measures 35
Part V.3. Summary of risk minimization measures 35
Part VI: Summary of the risk management plan Ziextenzo (pegfilgrastim) 36
I. The medicine and what it is used for 36
II. Risks associated with the medicine and activities to minimize or further characterize the risks 36
II.A List of important risks and missing information 37
II.B Summary of important risks 37
II.C Post-authorization development plan 37
II.C.1 Studies which are conditions of the marketing authorization 37
II.C.2. Other studies in post-authorization development plan 37
Part VII: Annexes 38
Annex 1 – EudraVigilance Interface 39
Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme 40
Annex 3 - Protocols for proposed, ongoing and completed studies in the pharmacovigilance plan 41
Annex 4 - Specific adverse drug reaction follow-up forms 42
A. Safety concern Capillary leak syndrome 42
B. Safety concern Cytokine release syndrome 45
Annex 5 - Protocols for proposed and ongoing studies in RMP part IV 48
Annex 6 - Details of proposed additional risk minimization activities (if applicable) 49
Annex 7 - Other supporting data (including referenced material) 50
Annex 8 - Summary of changes to the risk management plan over time 53

List of tables

Table 1 Part I.1 - Product Overview 7
Table 2 Key safety findings from nonclinical studies and relevance to human usage 10
Table 3 Safety concerns from nonclinical data 10
Table 4 Estimated cumulative subject exposure to LA-EP2006 in completed Sandoz clinical studies 12
Table 5 Cumulative subject exposure to LA-EP2006 in completed Sandoz clinical studies (LA-EP06-101, LA-EP06-106, and LA-EP06-104) in healthy subjects by age group and sex 13
Table 6 Cumulative exposure to LA-EP2006 in completed Sandoz clinical studies (LA-EP06-301 and LA-EP06-302) in patients with chemotherapy induced neutropenia by dose 13
Table 7 Cumulative exposure to LA-EP2006 in completed Sandoz clinical studies (LA-EP06-301 and LA-EP06-302) in patients with chemotherapy induced neutropenia by age group 14
Table 8 Cumulative exposure to LA-EP2006 in completed Sandoz clinical studies (LA-EP06-301 and LA-EP06-302) in patients with chemotherapy induced neutropenia by race ... 14
Table 9 Important exclusion criteria in pivotal studies in the development program 15
Table 10 Exposure of special populations included or not in clinical trial development programs..... 22
Table 11 Cumulative Patient Exposure from Marketing Experience (Presented in PTY) 24
Table 12 Important identified risk capillary leak syndrome: Other details 26
Table 13 Important identified risk acute respiratory distress syndrome: Other details 28
Table 14 Important potential risk cytokine release syndrome: Other details 30
Table 15 SVIII.1: Summary of safety concerns 32
Table 16 Summary of changes to the risk management plan over time 53

List of abbreviations

ADA	Adenosine Deaminase
ALT	Alanine Transaminase
ARDS	Acute respiratory distress syndrome
AST	Aspartate Transaminase
CHMP	Committee for Medicinal Products for Human Use
EC	Electronic Commission
EEA	European Economic Area
EMA	European Medicines Agency
EMEA	Europe, Middle East and Africa
EPAR	European public assessment report
EU	European Union
DDD	Defined Daily Dose
GCP	Good Clinical Practice
G-CSF	Granulocyte-colony stimulating factor
GVP	Good Pharmacovigilance Practices
HCP	Heaalthcare professional
HIV	Human immunodeficiency virus
INN	International Nonproprietary Name
LFT	Liver function tests
MAA	Marketing Authorization Application
MedDRA	Medical dictionary for regulatory activities
NHL	Non-Hodgkin's lymphoma
PD	Pharmacodynamics
PFS	Pre Filled Syringe
PK	Pharmacokinetics
PL	Patient leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PTY	Patient treatment year
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk Management Plan
SMQ	Standardized MedDRA Queries
SmPC	Summary of Product Characteristics
TAC	Taxane-Anthracycline-Cyclophosphamide
US	United States
WHO	World Health Organization
Note: The registered trademark sign "®" will be omitted for Ziextenzo and Neulasta to improved readability.	

Part I: Product(s) Overview

Table 1 Part I.1 - Product Overview

Active substance (International Nonproprietary Name or common name)	Pegfilgrastim
Pharmacotherapeutic group(s) (ATC Code)	Immunostimulants, colony stimulating factor; Anatomical Therapeutic Chemical (Classification System) (ATC): (L03AA13)
Marketing Authorization Holder	Sandoz
Medicinal products to which this RMP refers	1
Invented name in the European Economic Area (EEA)	Ziextenzo
Marketing authorization procedure	Centralized procedure
Brief description of the product	Chemical class: Immunostimulants, colony stimulating factor
	Summary of mode of action: Human granulocyte colony stimulating factor (G CSF) is a glycoprotein, which regulates the production and release of neutrophils from the bone marrow. Pegfilgrastim is a covalent conjugate of recombinant human G CSF (r metHuG CSF) with a single 20 kd polyethylene glycol molecule. Pegfilgrastim is a sustained duration form of filgrastim due to decreased renal clearance. Pegfilgrastim and filgrastim have been shown to have identical modes of action, causing a marked increase in peripheral blood neutrophil counts, with minor increases in monocytes and/or lymphocytes. Similarly to filgrastim, neutrophils produced in response to pegfilgrastim show normal or enhanced function as demonstrated by tests of chemotactic and phagocytic function.
	Important information about its composition: This medicinal product contains 30 mg sorbitol in each pre-filled syringe which is equivalent to 50 mg/mL. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account.
Hyperlink to the Product Information	[Ziextenzo Summary of Product Characteristics (SmPC) and Package leaflet (PL)]
Indication(s) in the EEA	Current: Reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).

	Proposed: Not applicable
Dosage in the EEA	Current: One 6 mg dose (a single pre-filled syringe) of Ziextenzo is recommended for each chemotherapy cycle, given at least 24 hours after cytotoxic chemotherapy. **<u>Method of administration</u>** Ziextenzo is for subcutaneous use. The injections should be given into the thigh, abdomen or upper arm. For detailed information on special populations- paediatric population and renal impairment and method of administration, please refer to the current SmPC.
	Proposed: Not applicable
Pharmaceutical form and strength	Current: Solution for injection in pre filled syringe (PFS); 6 mg
	Proposed: Not applicable
Is the product be subject to additional monitoring in the European Union (EU)	No

Part II Safety specification Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Not applicable.

Part II: Module SII - Non-clinical part of the safety specification

A high level summary of significant non-clinical safety findings from the development of Neulasta are summarized in Table 2. In line with the analytical and clinical evidence supporting the conclusion on biosimilarity, the general toxicity assessment performed on LA-EP2006 showed the same outcome as described for Neulasta. A summary on the safety concerns from a non-clinical perspective is summarized in Table 3.

Table 2 Key safety findings from nonclinical studies and relevance to human usage

Key safety findings (from non-clinical studies)	Relevance to human usage
Toxicity: • Extramedullary hematopoiesis and splenic enlargement	Splenic rupture, including fatal cases, can occur following the administration of Neulasta. Considering the high similarity of Neulasta and LA-EP2006 in general and with regard to the splenic enlargement observed in rats, it is expected that splenic rupture, including fatal cases, can occur following the administration of LA-EP2006 as well.
• Embryo-fetal toxicity (loss and malformations)	There are no or limited data on the safety of pegfilgrastim in pregnant women. Studies in animals have shown reproductive toxicity. Pegfilgrastim is not recommended during pregnancy or for women of childbearing potential who are not using contraception or only in the exceptional case that the benefit of treatment outweighs the risks for the embryo/fetus.

The clinical use of pegfilgrastim is well established. No new risks, unknown for reference product Neulasta-EU or necessitating further investigation, were identified during the non-clinical development of LA-EP2006. Taken together, there are no safety concerns for LA-EP2006 that are different from Neulasta EU.

Table 3 Safety concerns from nonclinical data

Safety concerns
Important identified risks (confirmed by clinical data) Severe splenomegaly/splenic rupture
Important potential risks (not refuted by clinical data or which are of unknown significance) None
Missing information Risks during pregnancy and lactation in humans

Part II: Module SIII - Clinical trial exposure

LA-EP2006 was developed as a biosimilar to the reference product Neulasta, which is authorized in the EU/EEA Amgen Europe B.V., The Netherlands (EMEA/H/C/000420). The clinical development program of LA-EP2006 consisted of 5 clinical studies. The results of these studies showed similarity between LA-EP2006 and Neulasta EU with respect to Pharmacokinetics (PK), Pharmacodynamics (PD), efficacy, safety and immunogenicity.

- Clinical Study Report of study LA-EP06-103: A randomized, double-blind, two-way crossover study to compare the pharmacokinetics, pharmacodynamics and safety of a single subcutaneous administration of LA-EP2006 and a single subcutaneous administration of Neulasta (EU-authorized) in healthy subjects.
- Clinical Study Report of study LA-EP06-101: Pharmacokinetic and pharmacodynamic comparison of LA-EP2006 with the reference product Neulasta (EU- and United States (US)-registered) after single dose subcutaneous application in healthy subjects.
- Clinical Study Report of study LA-EP06-104: A randomized, double-blind, three-way crossover study to compare the pharmacokinetics, pharmacodynamics and safety of a single 6 mg subcutaneous administration of the proposed biosimilar product LA-EP2006, Neulasta US and Neulasta EU in healthy subjects.
- Clinical Study Report of study LA-EP06-301: A randomized, double-blind, parallel-group, multi-centre Phase III comparative study investigating efficacy and safety of LA-EP2006 and Neulasta in breast cancer patients treated with myelosuppressive chemotherapy.
- Clinical Study Report of study LA-EP06-302: Pivotal study in breast cancer patients investigating efficacy and safety of LA-EP2006 and Neulasta.

In the pivotal randomized, double-blind, 2-period crossover PK/PD study LA-EP06-103 in healthy subjects, PK and PD similarity was demonstrated for LA-EP2006 and the reference product Neulasta EU. No meaningful differences regarding safety and immunogenicity were observed between LA-EP2006 and Neulasta EU. The study LA-EP06-101 was a single-dose, double-blind, 3-arm, parallel group PK/PD study conducted in healthy subjects comparing LA-EP2006 and Neulasta EU as well as for LA-EP2006 and Neulasta US, and Neulasta EU and Neulasta US. No meaningful differences regarding safety and immunogenicity were observed among the treatment groups. Similar efficacy and safety to Neulasta EU was demonstrated in two pivotal confirmatory safety and efficacy studies in breast cancer patients treated with myelosuppressive chemotherapy (studies LA-EP06-301 and LA-EP06-302).

The randomized, double-blind, 3-period crossover PK/PD study LA-EP06-104 in healthy subjects demonstrated PK and PD similarity between LA-EP2006, Neulasta EU, and Neulasta US. No meaningful differences regarding safety and immunogenicity were observed between the 3 products. This study was conducted for licensing of LA-EP2006 in the US and was not included in the LA-EP2006 Marketing Authorization Application (MAA) as it was completed after authorization of LA-EP2006 in the EU/EEA.

Neulasta is authorized in the EU for the *"reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes)."* LA-EP2006 was developed for the same indication, for the same population and for the same route of administration as the reference product.

Cumulative exposure to LA-EP2006 in the completed clinical studies with LA-EP2006 is summarized in the following tables.

Table 4 Estimated cumulative subject exposure to LA-EP2006 in completed Sandoz clinical studies

Study ID	Population	N	Days of exposure	Person-time (Patient-years)[1,2]
LA-EP06-101 (completed)	Healthy subjects	93	93	0.25
LA-EP06-103 (completed)	Healthy subjects	176	176	0.48
LA-EP06-104 (completed)	Healthy subjects	512	512	1.40
LA-EP06-301 (completed)	Patients with chemotherapy induced neutropenia	159	864	2.37
LA-EP06-302 (completed)	Patients with chemotherapy induced neutropenia	155	823	2.25
Total		**1095**	**2468**	**6.76**

N=number of subjects dosed with LA-EP2006 in a study

[1] These values are calculated as days/365.25 (days per year).

[2] The values in this column were calculated by using Excel. The added values may not match with the Total due to rounding.

Estimated cumulative exposure to LA-EP2006 by age and sex in completed Sandoz clinical studies in healthy subjects is summarized in the following table:

Table 5 Cumulative subject exposure to LA-EP2006 in completed Sandoz clinical studies (LA-EP06-101, LA-EP06-106, and LA-EP06-104) in healthy subjects by age group and sex

	N		Days of exposure		Person-time (Patient-years)[1,2]	
Age group	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
>10-20	29	30	29	30	0.08	0.08
>20-30	222	124	222	124	0.61	0.34
>30-40	116	59	116	59	0.32	0.16
>40-50	86	47	86	47	0.24	0.13
>50-60	43	25	43	25	0.12	0.07
Total	496	285	496	285	1.36	0.78

N=number of subjects dosed with LA-EP2006 in a study

[1] These values are calculated as days/365.25 (days per year).

[2] The values in this column were calculated by using Excel. The added values may not match with the Total due to rounding.

Cumulative exposure to LA-EP2006 in clinical studies LA-EP06-301 and LA-EP06-302 in patients with chemotherapy induced neutropenia is summarized in the following tables.

Table 6 Cumulative exposure to LA-EP2006 in completed Sandoz clinical studies (LA-EP06-301 and LA-EP06-302) in patients with chemotherapy induced neutropenia by dose

Dose (mg)	N	Days of exposure (days)	Patient-years (days/365.25)
6	11	11	0.03
12	7	14	0.04
18	8	24	0.07
24	18	72	0.20
30	54	270	0.74
36	216	1296	3.55

Pooled data from studies LA-EP06-301 and LA-EP06-302. Dose in the table equals to cycle, e.g. 12 mg=Cycle 2.

Days of exposure=total number of dose administrations; N=number of patients dosed

Table 7 Cumulative exposure to LA-EP2006 in completed Sandoz clinical studies (LA-EP06-301 and LA-EP06-302) in patients with chemotherapy induced neutropenia by age group

Age group (years)	N	Days of exposure (days)	Patient-years (days/365.25)
>10-20	0	0	0.00
>20-30	10	52	0.14
>30-40	57	312	0.85
>40-50	107	562	1.54
>50-60	95	527	1.44
>60-70	42	217	0.59
>70-80	3	17	0.05
Pooled data from studies LA-EP06-301 and LA-EP06-302. N=number of patients dosed Days of exposure=total number of dose administrations			

Table 8 Cumulative exposure to LA-EP2006 in completed Sandoz clinical studies (LA-EP06-301 and LA-EP06-302) in patients with chemotherapy induced neutropenia by race

Race	N	Days of exposure (days)	Patient-years (days/365.25)
White	219	1220	3.34
Asian	90	443	1.21
Black or African American	1	5	0.01
Other	4	19	0.05
Pooled data from studies LA-EP06-301 and LA-EP06-302 Days of exposure=total number of dose administrations			

Part II: Module SIV - Populations not studied in clinical trials

Since this (MAA) has been submitted for a similar biological medicinal product under Article 10(4) of Directive 2001/83/EC, as amended, a tailored clinical program was justified. Neulasta is authorized in the EU for the *"reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes)."* Two confirmatory efficacy and safety studies LA-EP06-301 and LA-EP06-302 were conducted in female breast cancer patients treated with myelosuppressive chemotherapy which induced neutropenia. The design, conduct, and therapeutic response rates of studies LA-EP06-301 and LA-EP06-302 were similar to those in historical clinical studies. Other patient populations were not studied in the LA-EP2006 development program.

Module SIV.1. Exclusion criteria in pivotal clinical studies within the development program

Table 9 Important exclusion criteria in pivotal studies in the development program

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Known hypersensitivity to *E. coli* proteins or any of the excipients used in the investigative medicinal product	Hypersensitivity may lead to potentially life-threatening anaphylactic reactions	No	In section 4.3 and 4.4 of the Neulasta SmPC, adequate warning and advice are given how to use pegfilgrastim in these patients. Hypersensitivity to the active substance or to any of the excipients is a contraindication to its use.
History of chronic myeloid leukemia or myelodysplastic syndrome	Neulasta is not authorized for use in patients with chronic myeloid leukemia and myelodysplastic syndrome.	No	In section 4.4 of the Neulasta SmPC further details are provided. The safety and efficacy of Neulasta have not been investigated in patients with myelodysplastic syndrome, chronic myelogenous leukemia, and in patients with secondary Acute Myeloid Leukemia; therefore, it should not be used in such patients. Particular care should be taken to distinguish the diagnosis of blast transformation of chronic myeloid leukemia from acute myeloid leukemia.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
History or presence of sickle cell disease	Sickle cell crises have been associated with the use of pegfilgrastim in patients with sickle cell trait or sickle cell disease	No	In sections 4.4 and 4.8 of the Neulasta SmPC, adequate warning and advice are given how to use pegfilgrastim in these patients.
Previous or concurrent malignancy except non-invasive non-melanomatous skin cancer, *in situ* carcinoma of the cervix, or other solid tumor treated curatively, and without evidence of recurrence for at least ten years prior to study entry	Previous treatment of these conditions has possibly involved chemotherapy with potential toxicity to bone marrow. For the purpose of a homogeneous, unimpaired bone marrow function at baseline of the clinical trials this factor was excluded. Additionally, any relapse independent of the treatment by G-CSF of these malignancies during the study should be excluded.	No	In section 4.4 of the Neulasta SmPC, adequate warning and advice are given how to use pegfilgrastim in these patients. In section 5.1 of the Neulasta SmPC the link between G-CSF and neutrophil release from the bone marrow is stated. Further it is indicated that G-CSF can promote growth of myeloid cells, including malignant cells, *in vitro* and similar effects may be seen on some non-myeloid cells *in vitro*.
Active uncontrolled infection	Chemotherapy as administered in the clinical trials is not indicated in patients with active uncontrolled infection. In healthy subject these infections might have impact on the absolute neutrophil count.	No	In section 4.1 of the Neulasta SmPC it is provided that the therapeutic indication of Neulasta is the reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukemia and myelodysplastic syndromes). This was placed in the protocols due to the impact from chemotherapy medications on subjects' morbidities.
Clinically significant impairment of left ventricular ejection fraction	This exclusion criterion was due to the chemotherapy scheme in breast cancer patients. Cardiac impairment is a known serious risk with anthracyclines, in particular doxorubicin.	No	An impact of left ventricular ejection fraction on the efficacy or safety of pegfilgrastim is not described or evident. There is no impact of left ventricular ejection fraction on the efficacy or safety of pegfilgrastim evident.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Severe heart valve disease, myocardial infarction, unstable angina pectoris, uncontrolled hypertension or uncontrolled arrhythmias within six months from study entry	This exclusion criterion was due to the Taxane-Anthracycline-Cyclophosphamide (TAC) chemotherapy scheme in breast cancer patients. Cardiac impairment is a known serious risk with anthracyclines, in particular doxorubicin.	No	An impact of these cardiac conditions on the efficacy or safety of pegfilgrastim is not described or evident.
Significant neurologic or psychiatric disorders including psychotic disorders, dementia or seizures that would have prohibited the understanding and giving of informed consent	Informed consent is an essential part of clinical trials and Good Clinical Practice (GCP). Patients cannot participate without informed consent.	No	An impact of neurologic or psychiatric disorders on the efficacy or safety of pegfilgrastim is not described or evident.
Concurrent or prior radiotherapy within four weeks of randomization	Previous radiotherapy could have impaired bone marrow function. For the purpose of a homogeneous, unimpaired bone marrow function at baseline of the clinical trials this factor was excluded.	No	In section 5.1 of the Neulasta SmPC the link between G-CSF and neutrophil release from the bone marrow is stated.
Concurrent or prior chemotherapy for breast cancer	Chemotherapy is potentially toxic to bone marrow. For the purpose of a homogeneous, unimpaired bone marrow function at baseline of the clinical trials this factor was excluded.	No	In section 5.1 of the Neulasta SmPC the link between G-CSF and neutrophil release from the bone marrow is stated.
Concurrent or prior anti-cancer treatment for breast cancer such as endocrine therapy, immunotherapy,	These treatments could be potentially toxic to bone marrow. For the purpose of a homogeneous, unimpaired bone marrow	No	In section 5.1 of the Neulasta SmPC the link between G-CSF and neutrophil release from the bone marrow is stated.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
monoclonal antibodies and/or biological therapy	function at baseline of the clinical trials this factor was excluded.		
Concurrent prophylactic antibiotics	Febrile neutropenia and the duration of neutropenia were endpoints of the clinical trials. Concurrent antibiotics at inclusion would have interfered with this study objective and bias the study.	No	In section 4.1 of the Neulasta SmPC it is provided that the therapeutic indication of Neulasta is the reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).
Prior bone marrow or stem cell transplant	These treatments had most likely involved chemotherapy with potential toxicity to bone marrow. For the purpose of a homogeneous, unimpaired bone marrow function at baseline of the clinical trials this factor was excluded.	No	In section 5.1 of the Neulasta SmPC the link between G-CSF and neutrophil release from the bone marrow is stated.
Previous therapy with any rhG-CSF product	Previous therapy with such products may increase the risk of hypersensitivity or lead to otherwise altered treatment response. For the purpose of a homogeneous, unimpaired bone marrow function at baseline of the clinical trials this factor was excluded.	No	In section 4.3 and 4.4 of the Neulasta SmPC, adequate warning and advice are given how to use pegfilgrastim in these patients. Hypersensitivity to the active substance or to any of the excipients is provided as contraindication. Additionally, in section 5.1 of the Neulasta SmPC the link between G-CSF and neutrophil release from the bone marrow is stated.
Patient known to have human immunodeficiency virus (HIV), Hepatitis B, Hepatitis C or who had a positive serology for HIV, Hepatitis B or	Such patients are likely to have an impaired bone marrow function. For the purpose of a homogeneous, unimpaired bone marrow function at baseline of the clinical trials this factor was excluded. Patients with hepatitis	No	In section 5.1 of the Neulasta SmPC the link between G-CSF and neutrophil release from the bone marrow is stated.In section 4.8 of the Neulasta SmPC a transient elevation in liver function test (LFTs) for Alanine Transaminase (ALT) or Aspartate Transaminase (AST) is stated. Uncommon elevations in LFTs for

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Hepatitis C at screening	could present independent of treatment with G-CSF elevations in liver function test, which in turn might bias safety readout during the study.		ALT (alanine aminotransferase) or AST (aspartate aminotransferase), have been observed in patients after receiving pegfilgrastim following cytotoxic chemotherapy. These elevations are transient and return to baseline.
Known active drug addiction, including alcoholism	These conditions were excluded because they are known to significantly increase the drop-out risk.	No	An impact of the drug addiction on the efficacy or safety of pegfilgrastim is not described or evident.
Positive testing for Adenosine Deaminase (ADA) at Screening.	The pre-existence of ADA might have an impact on the efficiency and safety during the study and therefore interfered with the study objective.	No	In section 4.4 of the Neulasta SmPC, adequate warning and advice are given how to use pegfilgrastim in these patients.
Participation in any other clinical study using an investigational medicinal product or device within three months before the screening visit	This is an essential condition for all clinical trials according to GCP.	No	Not applicable
For all women of childbearing potential: negative serum pregnancy test within seven days prior to randomization, and using a highly effective method of birth control	Pregnancy is a contraindication to chemotherapy	Yes	The SmPCs of docetaxel, doxorubicin and cyclophosphamide indicate that these products may cause fetal harm when administered to pregnant women therefore use is not recommended.

Module SIV.2. Limitations to detect adverse reactions in clinical trial development programs

In the LA-EP2006 clinical development program, 314 female breast cancer patients with chemotherapy-induced neutropenia and 781 healthy subjects received LA-EP2006. This clinical experience may be insufficient to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by cumulative

exposure. The number of patients exposed to LA-EP2006 (314 patients) is considered sufficient to detect adverse reactions to the reference product with a true frequency greater than 1 in 136 (using the N/3 rule). The maximum observation period was about 10 months. Potential longer-term risks are not known. The maximum duration of LA-EP2006 exposure was over six chemotherapy cycles (one injection per cycle) with 3 weeks intervals. Additional risks for patients receiving higher numbers of treatment cycles are unclear.

The existing clinical study experience also may be insufficient to detect rare differences in adverse reactions between LA-EP2006 and the reference product. Rare in terms of pharmacovigilance means an event with a probability between 0.01% and 0.1%. LA-EP2006 showed a similar PK and safety profile to that of the reference product as directly shown in the LA-EP2006 nonclinical program. LA-EP2006 also showed a similar PK and safety profile to the reference product in the LA-EP2006 clinical development program. Thus, it is justified to build upon the clinical study experience that has accumulated for the reference product.

Children

The safety and efficacy of LA-EP2006 and the reference medicinal product Neulasta are similar. For the development of LA-EP2006 no studies in children were performed or are warranted.

The efficacy, safety, and PK of the reference product Neulasta in children was evaluated in a multicenter, randomized, open-label study, in which paediatric subjects with sarcoma were randomized in a 6:1 allocation to receive either a single dose of pegfilgrastim 100 µg/kg or daily doses of filgrastim 5 µg/kg after the completion of vincristine, doxorubicin, cyclophosphamide, etoposide, and ifosfamide (VAdriaC/IE) chemotherapy (European Assessment Report 2013).

Forty-four subjects were enrolled (n = 38 pegfilgrastim, 6 filgrastim) at 10 study centers in the US and Australia. All but 1 subject received at least 1 dose of pegfilgrastim or filgrastim (37 pegfilgrastim, 6 filgrastim).

Thirteen subjects (12 pegfilgrastim, 1 filgrastim) were enrolled in the 0- to 5-year age group, 12 subjects (10 pegfilgrastim, 2 filgrastim) in the 6- to 11-year group, and 19 subjects (16 pegfilgrastim, 3 filgrastim) in the 12- to 21-year group.

As summarized in the SmPC (2023), a higher frequency of serious adverse reactions in younger children aged 0-5 years (92%) has been observed compared to older children aged 6-11 and 12-21 years respectively (80% and 67%) and adults. The most common adverse reaction reported was bone pain.

Elderly

For the development of LA-EP2006, special studies in old or very old patients were not conducted. In a subgroup analysis by age (≤65 years and >65 years) of the studies LA-EP06-301 and LA-EP06-302 the number of patients ≤65 years of age treated with LA-EP2006 were: 301; the number of patients > 65 years of age was 13. In both age groups, the incidences of treatment-emergent adverse events were similar.

The reference product Neulasta was administered in patients >65 years of age. A clinical study evaluated the incidence of febrile neutropenia and related events in elderly cancer patients receiving pegfilgrastim beginning with Cycle 1 (proactive) in comparison with pegfilgrastim initiated after Cycle 1 at the physician's discretion (reactive). Patients with either solid tumors or non-Hodgkin's lymphoma (NHL) were randomly assigned to receive pegfilgrastim either proactively or reactively. The primary endpoint was the proportion of patients experiencing febrile neutropenia. There were 852 patients enrolled (median age, 72 years). Proactive pegfilgrastim use resulted in a significantly lower incidence of febrile neutropenia for both solid tumor and NHL patients compared with reactive use. Proactive pegfilgrastim use also led to fewer hospitalizations resulting from neutropenia and febrile neutropenia by approximately 50% (Balducci et al 2007).

Data of the reference product Neulasta (European Assessment Report 2013) show that within age groups (< 65 years of age and ≥65 years), the overall incidence of adverse events was similar between filgrastim and pegfilgrastim. Data from 85 patients, ≥65 years of age, in the pegfilgrastim group did not suggest a contraindication for the use of pegfilgrastim in an elderly population.

Pregnant or breast feeding women

There are no or limited amount of data from the use of pegfilgrastim in pregnant women.

Pregnant or breast feeding women have not been included in clinical trials with LA-EP2006. For studies with new investigational medicinal products in healthy volunteers pregnancy or breast feeding are strict exclusion criteria.

For patients needing chemotherapy such as the TAC scheme for breast cancer in the clinical trials with pegfilgrastim, breast feeding is a contraindication originating from the chemotherapy.

According to the SmPC (2023), there is insufficient information on the excretion of Neulasta/metabolites in human milk; a risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Neulasta therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Patients with hepatic impairment

No specific studies for LA-EP2006 or for Neulasta have been conducted in patients with hepatic impairment. According to the SmPC (2023), due to the neutrophil-mediated clearance mechanism, the PK of pegfilgrastim is not expected to be affected by renal or hepatic impairment.

Patients with renal impairment

No specific studies for LA-EP2006 have been conducted in patients with renal impairment. According to the SmPC (2023), due to the neutrophil-mediated clearance mechanism, the pharmacokinetics of LA-EP2006 is not expected to be affected by renal or hepatic impairment. In an open label, single dose study (n = 31) with Neulasta, various stages of renal impairment, including end-stage renal disease, had no impact on the pharmacokinetics of pegfilgrastim (Yang et al 2008).

Patients with cardiac impairment

No specific studies for LA-EP2006 have been conducted in patients with cardiac impairment.

Patients with pulmonary impairment

No specific studies for LA-EP2006 and for Neulasta have been conducted in patients with pulmonary impairment.

Patients with a disease severity different from the inclusion criteria in the clinical trial population

No specific studies have been conducted in patients with a disease severity different from the inclusion criteria in the clinical trial population.

Sub-populations carrying known and relevant polymorphisms

Not applicable

Patients of different racial and/or ethnic origin

Patients with different racial and/or ethnic origin have been included in clinical studies with LA-EP2006 or the reference product Neulasta. The latter is used clinically worldwide. There is no evidence that racial or ethnic factors have any impact on the benefits or risks of pegfilgrastim.

Module SIV.3. Limitations in respect to populations typically underrepresented in clinical trial development programs

Table 10 Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	Not included in the clinical development program
Patients with relevant comorbidities: • Patients with hepatic impairment	Not included in the clinical development program

<table>
<tr><th>Type of special population</th><th>Exposure</th></tr>
<tr><td>• Patients with renal impairment
• Patients with cardiovascular impairment
• Immunocompromised patients
• Patients with a disease severity different from inclusion criteria in clinical trials</td><td></td></tr>
<tr><td>• Subpopulations carrying relevant genetic polymorphisms</td><td>Not included in the clinical development program</td></tr>
<tr><td>Other:
• Children
• Elderly</td><td>Not included in the clinical development program
45 patients >60 years with chemotherapy induced neutropenia:
<table><tr><th>Age (years)</th><th>N</th><th>Person-years (days/365.25)</th></tr><tr><td>>60-70</td><td>42</td><td>0.59</td></tr><tr><td>>70-80</td><td>3</td><td>0.05</td></tr></table></td></tr>
</table>

Part II: Module - SV: Post-authorization experience

SV.1. Post-authorization exposure

SV.1.1 Method used to calculate exposure

An estimate of patient exposure is calculated based on worldwide sales volume of pre-filled syringes in mg of active substance sold during the reporting interval and cumulatively and the Defined Daily Dose (DDD) using the formula.

An estimate of patient exposure is calculated based on worldwide sales volume of PFS of active substance sold during the reporting interval and the DDD using the formula:

Estimated exposure in patient treatment years (PTYs)= $\frac{\text{Number of syringes *6 mg (1 PFS)}}{\text{DDD } \left(\frac{\text{mg}}{\text{day}}\right) * 365 \text{ days/Year}}$.

The recommended dose of pegfilgrastim is one 6 mg pre-filled syringe for each chemotherapy cycle, given at least 24 hours after the start of cytotoxic chemotherapy. Assuming the duration of a chemotherapy cycle to be 21 days and since pegfilgrastim is given 24 hours after start of the chemotherapy cycle, the DDD is calculated to be 6/20 = 0.3 mg.

SV.1.2. Exposure

During the reporting interval and cumulatively, worldwide patient exposure was estimated to be 1,24,567 PTY for pegfilgrastim. (Table 11).

Table 11 Cumulative Patient Exposure from Marketing Experience (Presented in PTY)

Country	Cumulative Exposure till data lock point (31 Dec 2025)	
	Amount sold (mg)	Estimated exposure (PTY)*
EEA	9,056,238	82,705
Japan	-	-
Rest of the World	1,841,373	16,816
US and Canada	2,742,449	25,045
Total	13,640,060	1,24,567

Source of data: Worldwide sales volume. The values in above tables are calculated by using formulas in excel.
*The sum up values may not match with the total as the figures are rounded off to nearest digit.

The patient exposure based on demographics (i.e., age, sex, dose and indication) could not be estimated, as the data based on demographics is not available.

Part II: Module - SVI: Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

No evidence to suggest a potential for drug abuse or misuse has been observed.

Part II: Module SVII - Identified and potential risks

Part II SVII.1. Identification of safety concerns in the initial RMP submission

Not applicable.

Part II SVII.2: New safety concerns and reclassification with a submission of an updated RMP

'Sickle cell crisis in patients with sickle cell disease' and 'Glomerulonephritis' which were previously classified as important identified risks are removed from the list of safety concerns.

Reason for the removal of the list of safety concerns:

The above mentioned important identified risks have been removed to align with the reference product Neulasta's (pegfilgrastim) RMP v. 11.0 dated 20 May 2025.

Part II SVII.3: Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important Identified Risk: Capillary leak syndrome

Capillary leak syndrome has not been observed in clinical studies with LA-EP2006.

Table 12 Important identified risk capillary leak syndrome: Other details

Capillary leak syndrome	Details
Medical dictionary for regulatory activities (MedDRA) search terms for spontaneous post-marketing data	Standardized MedDRA Queries (SMQ): Haemodynamic oedema, effusions and fluid overload
Potential mechanisms	Several hypotheses have been proposed, including a direct endothelial effect of G-CSF, or a neutrophil activation cascade with release of inflammatory mediators. Capillary leak syndrome has been described in healthy donors free of any risk factor other than apheresis; it has been hypothesized that G-CSF stimulation in conjunction with marked neutrophilia and apheresis could trigger leukocyte activation and production of inflammatory mediators resulting in tissue injury. In cancer patients receiving G-CSF, aggressive chemotherapy damaging the endothelial cells and sepsis-related vascular injury could favor endothelial dysfunctions involving G-CSF and/or activated neutrophils. (Neulasta RMP v11.0)

Capillary leak syndrome	Details
Evidence source(s) and strength of evidence	Capillary leak syndrome is listed in section 4.4 Special warnings and precautions and section 4.8 Undesirable effects of the SmPC (2023) and is therefore considered as an important identified risk of LA-EP2006.
Characterization of the risk:	Capillary leak syndrome has not been observed in clinical studies with LA-EP2006. In the SmPC (2023), the frequency of the respective risk is specified as "uncommon" (≥1/1,000 to <1/100). Capillary leak syndrome has been reported after G-CSF administration and is characterized by hypotension, hypoalbuminemia, edema and hemo-concentration. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care (SmPC 2023). Cases of capillary leak syndrome have been reported in the post marketing setting with G-CSF use. These have generally occurred in patients with advanced malignant diseases, sepsis, taking multiple chemotherapy medications or undergoing apheresis. Capillary leak syndrome is characterized by self-reversing episodes during which the endothelial cells which line the capillaries separate for a few days, allowing for a leakage of fluid from the circulatory system to the interstitial space, resulting in a dangerous hypotension (low blood pressure), hemo-concentration, and hypoalbuminemia. It is a life-threatening illness because each episode has the potential to cause damage to, or the failure of, vital organs due to limited perfusion (Kapoor et al 2010). Most patients report having a runny nose and/or other flu-like symptoms, or else gastro-intestinal disorders (diarrhea or vomiting), or a general weakness or pain in their limbs, but others get no particular or consistent warning signs ahead of their episode. They subsequently develop thirst and light-headedness, hemo-concentration, low blood pressure (hypotension), hypoalbuminemia, partial or generalized edema, organ failure, and potentially fatal outcome. As of 31 Dec 2025, cumulatively 19 post marketing cases were retrieved for the risk capillary leak syndrome. Among which 18 were Healthcare professionals (HCP) and 01 was non-HCP; 14 were serious and 05 were non-serious cases reporting 21 events of interest (11 serious and 10 non-serious). There were no fatal or life-threatening cases reported. Review of the cases did not identify any new significant safety information.
Risk factors and risk groups	Multiple drug therapy, cancer patients receiving chemotherapy, middle age
Preventability	A recent review of clinical experience with 28 European systemic capillary leak syndrome patients suggests that prophylactic treatment may reduce the frequency and severity of attacks and may improve survival (Gousseff et al 2011).
Impact on the benefit-risk balance of the product	The totality of the evidence established similarity of LA-EP2006 to the reference product Neulasta EU in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise as required by CHMP/437/04 Rev 1. Overall, the results of the global development program confirm that LA-EP2006 is biosimilar to the reference product Neulasta EU and has a similar and positive benefit-risk ratio.

Capillary leak syndrome	Details
Public health impact	The impact on public health is not known, but it is low.

Important Identified Risk: Acute respiratory distress syndrome

Acute Respiratory Distress Syndrome (ARDS) has not been observed in clinical studies with LA-EP2006.

Table 13 Important identified risk acute respiratory distress syndrome: Other details

Acute respiratory distress syndrome	Details
MedDRA search terms for spontaneous post-marketing data	SMQ (narrow): Eosinophilic pneumonia, Interstitial lung disease and Acute central respiratory depression High Level Term: Lower respiratory tract inflammatory and immunologic conditions.
Potential mechanisms	The pathogenesis of ARDS is complex and probably involves multiple mechanisms, including prostaglandin release and complement activation, that lead to the sequestration of neutrophils in areas of inflammation in the pulmonary microvasculature, with resultant pulmonary dysfunction. (Neulasta RMP)
Evidence source(s) and strength of evidence	Acute respiratory distress syndrome (ARDS) is described under 'Pulmonary adverse events' in section 4.4 Special warnings and precautions and listed in section 4.8 Undesirable effects of the SmPC (2023) and is therefore considered as an important identified risk of LA-EP2006.
Characterization of the risk:	Serious pulmonary adverse events were reported from clinical studies with LA-EP2006. In the SmPC (2023) the frequency of the ARDS is specified as "uncommon" (≥1/1,000 to <1/100). The first study to use the current definitions was performed in Scandinavia, which reported annual rates of 17.9 cases per 100,000 population for acute lung injury and 13.5 cases per 100,000 population for ARDS (Luhr et al 1999). A prospective study using the 1994 American European Consensus Conference definition was performed in King County, Washington, from April 1999 through July 2000 and found that the age-adjusted incidence of acute lung injury was 86.2 per 100,000 person-years (Rubenfeld et al 2005). Incidence increased with age, reaching 306 per 100,000 person-years for people in aged 75-84 years. The onset of pulmonary signs such as cough, fever, and dyspnoea in association with radiological signs of pulmonary infiltrates, and deterioration in pulmonary function along with increased neutrophil count may be preliminary signs of ARDS. In such circumstances pegfilgrastimshould be discontinued at the discretion of the physician and the appropriate treatment given (SmPC 2023). Mortality to ARDS is in the range of 30-40% (Davey-Quinn et al 1999, Davidson et al 1999). Survivors of ARDS have significant functional impairment for years following recovery.

Acute respiratory distress syndrome	Details
	Most patients with interstitial pneumonia describe an upper respiratory infection/viral-like prodrome and a non-productive cough. A bimodal distribution appears to exist, with about 50% of patients presenting with symptoms of dyspnoea within the first week of symptoms and others presenting after at least a month and up to 60 days from the onset of symptoms (Vourlekis 2004). Patients frequently progress rapidly from shortness of breath to hypoxemic respiratory failure that requires prolonged mechanical ventilation. Survival data are limited and likely subject to some study bias, but the acute case fatality ratio is estimated to be 50% or more (Vourlekis 2004, Travis et al 2013). Most deaths occur within 1-3 months of diagnosis. Patients developing ARDS are critically ill, often with multisystem organ failure, and they may not be capable of providing historical information. Typically, the illness develops within 12-48 hours after the inciting event, although, in rare instances, it may take up to a few days. With the onset of lung injury, patients initially note dyspnoea with exertion. This rapidly progresses to severe dyspnoea at rest, tachypnoea, anxiety, agitation, and the need for increasingly high concentrations of inspired oxygen. Morbidity is considerable. Patients with ARDS are likely to have prolonged hospital courses, and they frequently develop nosocomial infections, especially ventilator-associated pneumonia. In addition, patients often have significant weight loss and muscle weakness, and functional impairment may persist for months after hospital discharge (Wang et al 2014). As of 31 Dec 2025, cumulatively 11 serious HCP post marketing cases were retrieved with 05 serious events of interest. Among these, two fatal cases and two LT cases were reported. Review of the cases did not identify any new significant safety information.
Risk factors and risk groups	Acute respiratory distress syndrome (ARDS) may occur in people of any age. The incidence for interstitial lung disease ranges from 3.62 to 25.8 per 100,000 inhabitants/year (Lopez-Campos et al 2004, Xaubet et al 2004, Karakatsani et al 2009, Hyldgaard et al 2014, Musselim et al 2013, Duchemann et al 2017). Acute respiratory distress syndrome (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.
Preventability	Although multiple risk factors for ARDS are known, no successful preventive measures have been identified. As per SmPC (2023), in case of suspected ARDS, pegfilgrastim should be discontinued.
Impact on the benefit-risk balance of the product	The totality of the evidence established similarity of LA-EP2006 to the reference product Neulasta EU in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise as required by CHMP/437/04 Rev 1. Overall, the results of the global development program confirm that LA-EP2006 is biosimilar to the reference product Neulasta EU and has a similar and positive benefit-risk ratio.
Public health impact	The impact on public health is not known, but it is low.

Important Potential Risk: Cytokine release syndrome

Cytokine release syndrome has not been observed in clinical studies with LA-EP2006.

Table 14 Important potential risk cytokine release syndrome: Other details

Cytokine release syndrome	Details
MedDRA search terms for spontaneous post-marketing data	Preferred Term: Cytokine release syndrome, Cytokine storm, Shock, Macrophage activation, Haemophagocytic lymphohistiocytosis, and Systemic inflammatory response syndrome
Potential mechanisms	Some monocyte/macrophages populations are reported to express G-CSF-R and may be able to respond to G-CSF through cytokine upregulation (Boneberg et al 2000). However, several studies evaluating monocyte cytokine release report that G-CSF treatment resulted in a decrease in pro-inflammatory cytokine production (Hartung et al 1995a, Hartung et al 1995b, Pajkrt et al 1997, Boneberg et al 2000). Authors of one study (Boneberg et al 2000) proposed that attenuation of the inflammatory response would be protective against fatal over activation of the immune system. This hypothesis was supported by Görgen et al (1992), who demonstrated that G-CSF treatment was protective in both rat and mouse models of septic shock. ln this study, increased G-CSF dose was associated with increased suppression of the pro-inflammatory cytokine, tumor necrosis factor-alpha and decreased mortality (mortality: 83% in control animals, 33% in animals treated with 50 µg/kg G-CSF, 0% in animals treated with 250 µg/kg G-CSF) (Görgen et al 1992). ln a separate study by Fink et al (1993), lung injury was reduced by G-CSF pre-treatment in lipopolysaccharide-challenged pigs.
Evidence source(s) and strength of evidence	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 Pharmacovigilance Risk Assessment Committee (PRAC) (EMA/PRAC/693228/2013, EMA/PRAC/720475/2013/Rev. 1), after their due consideration of the available evidence from case reports in EudraVigilance and the scientific literature.
Characterization of the risk:	Cytokine release syndrome has not been observed in clinical studies with LA-EP2006). No information on background rates is available for the target populations for filgrastim. With monoclonal antibody treatment, Grade 3 or 4 infusion reactions occur at an average rate of 3% in the US, and at a rate of 22% in selected centers in Tennessee and North Carolina (O'Neil 2010). Cytokine release syndrome is a rapid, uncontrolled hyper-cytokinemia that results in a range of clinical effects from pyrexia and fatigue to multiple organ failure in association with therapeutic infusion of antibodies (e.g. rituximab, trastuzumab). Mechanism of action for cytokine release syndrome involves targeted activation of immune cells and elevation of both pro-inflammatory (e.g. tumor necrosis factor-alpha) and anti-inflammatory (e.g. interleukin-10) cytokines (Dillman 1999, Winkler et al 1999, Chung 2008, O'Neil 2010). Clinical manifestation may include

Cytokine release syndrome	Details
	non-specific symptoms, such as nausea, headache, tachycardia, hypotension, rash, and shortness of breath. The syndrome is typified by the appearance of plasma cytokines within a few hours of infusion of the antibody (Wing 2008). Signs and symptoms of cytokine release syndrome generally occur acutely, within minutes to a few hours after first dose administration of the drug, and the events are mostly clinically indistinguishable from an acute lgE mediated anaphylactic or non-lgE mediated anaphylactoid reaction (Kang and Saif 2007, O'Neil 2010). Monoclonal antibodies used in the treatment of cancers such as rituximab, trastuzumab, bevacizumab, and cetuximab are commonly associated with infusion-related reactions secondary to the release of inflammatory cytokines, or the occurrence of tumor Iysis syndrome, that involve cytokine release from malignant cells targeted by these monoclonal antibodies (Kang and Saif 2007, Howard et al 2011). Pegfilgrastim is not a monoclonal antibody and has no receptors to T-cells or B-cells. Most patients experience a mild to moderate reaction; however, the reaction may be severe and life-threatening. As of 31 Dec 2025, cumulatively no relevant post marketing cases were retrieved for the risk of cytokine release syndrome.
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 (Chung 2008). 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) (Winkler et al 1999). 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 (Vogel 2010). Geographic location may elevate the risk for an infusion reaction from cetuximab (O'Neil 2010).
Preventability	No information on preventability is available.
Impact on the benefit-risk balance of the product	The totality of the evidence established similarity of LA-EP2006 to the reference product Neulasta EU in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise as required by CHMP/437/04 Rev 1. Overall, the results of the global development program confirm that LA-EP2006 is biosimilar to the reference product Neulasta EU and has a similar and positive benefit-risk ratio.
Public health impact	Based on the large body of knowledge from the clinical trial and post-marketing settings, the public health impact is considered to be low.

SVII.3.2. Presentation of the missing information

None

Part II: Module SVIII - Summary of the safety concerns

Table 15 SVIII.1: Summary of safety concerns*

Important identified risks	Capillary leak syndrome Acute respiratory distress syndrome
Important potential risks	Cytokine release syndrome
Missing information	None

* The summary of safety concerns has been aligned to the reference product Neulasta's (Pegfilgrastim) RMP v11.0 dated 20 May 2025.

Part III: Pharmacovigilance plan (including post-authorization safety studies)

Part III.1. Routine pharmacovigilance activities

No special important risks have been identified for pegfilgrastim which require additional pharmacovigilance activities other than routine pharmacovigilance.

The global pharmacovigilance system ensures the services of a Qualified Person responsible for Pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the community or in a third country.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnairesfor the following risks:

- Capillary leak syndrome
- Cytokine release syndrome

The specific adverse reaction follow-up forms are provided to the reporters in order to obtain structured information on reported suspected adverse reactions of special interest.

The specific adverse reaction follow-up forms are provided in Annex 4.

Follow-up of case reports: The minimum desired case information for pegfilgrastim includes the brand name and batch number of the suspect product. Additional efforts must be made to collect this information in accordance with Good Pharmacovigilance Practices (GVP) VI.

Other forms of routine pharmacovigilance activities:

None.

Part III.2. Additional pharmacovigilance activities

There are no planned, ongoing or completed additional pharmacovigilance activities.

Part III.3. Summary Table of additional pharmacovigilance activities

Not applicable.

Part IV: Plans for post-authorization efficacy studies

No post-authorization efficacy studies are in place or planned.

Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

Risk Minimization Plan

The safety information in the proposed product information is aligned to the reference medicinal product.

Part V.1. Routine risk minimization measures

Not applicable.

Part V.2. Additional Risk minimization measures

Not applicable.

Part V.3. Summary of risk minimization measures

Not applicable.

Part VI: Summary of the risk management plan 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 authorized for reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes). It contains pegfilgrastim as the active substance and it is given by subcutaneous injection.

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, under the medicine's webpage Ziextenzo | European Medicines Agency (EMA).

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 Periodic Safety Update Report 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 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	
Important identified risks	Capillary leak syndrome Acute respiratory distress syndrome
Important potential risks	Cytokine release syndrome
Missing information	None

II.B Summary of important risks

The safety information in the proposed product information is aligned to the reference medicinal product.

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.

Annex 4 - Specific adverse drug reaction follow-up forms

A. Safety concern Capillary leak syndrome

SANDOZ

Manufacturer Receipt Date (dd/mmm/yyyy): *Argus case ID:* _____

_____/_____/_____

Targeted Follow-up Checklist
Pegfilgrastim 6 mg / 0.6 ml solution for injection
Capillary Leak Syndrome

If there is the possibility of capillary leak syndrome, in addition to collecting routine information for this adverse event please ensure the following additional information is provided and/or confirmed.

Patient date of birth **Patient age** **Patient gender** **Patient weight**

☐ **Male** ☐ **Female** _____lbs ____kg

Pregnant: ☐ **Yes** ☐ **No**

White cell count before event: _____x10^9/L **Provide date** _____

Disease and therapy data:

Brand name of the pegfilgrastim product administered

☐ Ziextenzo

☐ Other:_____

Use of Pegfilgrastim 6 mg / 0.6 ml solution for injection:

Start: _____ Stop: _____

Last dose received (mcg): _____Batch/Lot#: _____

Action taken:

☐ **None** ☐ **Dose reduced** ☐ **Dose increased** ☐ **Drug withdrawn** ☐ **Drug re-challenged**

Indication: _____

Route of administration: ☐ **Subcutaneous** ☐ **Other (Specify):**

_____

Patient History:

Has the patient currently or had the patient a history of any of the following? **Check all that applies.**

- ☐ Previous history of capillary leak syndrome
- ☐ Any history of blood/bone marrow stem cell transplant
- ☐ History of use of steroids/immunosuppressants
- ☐ Any history of cytokine reaction after biologic agents
- ☐ Other relevant history and comorbidities *(please specify)*

Please specify relevant conditions: _____

_____

_____

Has the patient taken any medications in reasonably close proximity to the event which could have contributed to the adverse event? **Please specify (include name, start and stop dates, dosage and indication).**

_____

_____

Event Description:

Did the patient present with any of the following signs or symptoms? **Check all that applies**

- ☐ Hypovolemic shock
- ☐ Congestive heart failure
- ☐ Blood pressure
- ☐ Edema
- ☐ Dyspnea
- ☐ Tachypnea
- ☐ Ascites
- ☐ None of the above
- ☐ Others

Please describe the symptoms with time to onset from Pegfilgrastim introduction, duration, treatment and outcome. Please provide discharge summary if available/applicable:

_____

_____

_____

_____

If the patient died please provide the cause and date of death: _____

Was an autopsy performed? ☐ **Yes** ☐ **No**

If yes, please provide autopsy results: _____

Diagnostic Tests: Please specify relevant investigations and tests (e.g. chest x-ray, echocardiogram, chest Computed Tomography, etc.) with name, date of tests and findings / values (please attach available reports):

_____

_____

_____

_____

_____

REPORTER Name: _____
State/Province: _____
Country/Postal Code: _____
Phone: (include country code): _____
Signature: _____
Title: _____ Date:
_____

(TFuQ on Capillary leak syndrome version 2.1)

B. Safety concern Cytokine release syndrome

SANDOZ

Manufacturer Receipt Date (dd/mmm/yyyy): *Argus case ID:* _____

_____/_____/_____

Targeted Follow-up Checklist
Pegfilgrastim 6 mg / 0.6 ml solution for injection
Cytokine Release Syndrome

If there is the possibility of cytokine release syndrome, in addition to collecting routine information for this adverse event please ensure the following additional information is provided and/or confirmed.

Patient date of birth	**Patient age**	**Patient gender**	**Patient weight**
		☐ **Male** ☐ **Female**	_____lbs ____kg
Pregnant:	☐ **Yes**	☐ **No**	

White cell count before event: _____x10^9/L **Provide date** _____

Disease and therapy data:

Brand name of the pegfilgrastim product administered

☐ Ziextenzo

☐ Other:_____

Use of Pegfilgrastim 6 mg / 0.6 ml solution for injection:

Start: _____Stop: _____

Last dose received (mcg): _____Batch/Lot#: _____

Action taken:

☐ **None** ☐ **Dose reduced** ☐ **Dose increased** ☐ **Drug withdrawn** ☐ **Drug re-challenged**

Indication: _____

Route of administration: ☐ **Subcutaneous** ☐ **Other (Specify)**

Patient History:

Has the patient currently or had the patient a history of any of the following? **Check all that applies.**

- ☐ Previous history of capillary leak syndrome
- ☐ Any history of blood/bone marrow stem cell transplant
- ☐ History of use of steroids/immunosuppressants
- ☐ Any history of cytokine reaction after biologic agents
- ☐ Other relevant history and comorbidities *(please specify)*

Please specify relevant conditions: _____

_____

_____

Has the patient taken any medications in reasonably close proximity to the event which could have contributed to the adverse event? **Please specify (include name, start and stop dates, dosage and indication).**

_____

_____

Event Description:

Did the patient present with any of the following signs or symptoms? **Check all that applies**

- ☐ Multiple organ failure
- ☐ Fever/chills
- ☐ Headache
- ☐ Chest pain
- ☐ Blood pressure
- ☐ Dyspnea
- ☐ Tachypnea
- ☐ Edema
- ☐ None of the above
- ☐ Others

Please describe the symptoms with time to onset from Pegfilgrastim introduction, duration, treatment and outcome. Please provide discharge summary if available/applicable:

_____

_____

_____

_____

If the patient died please provide the cause and date of death: _____

Was an autopsy performed? ☐ **Yes** ☐ **No**

If yes, please provide autopsy results: _____

Diagnostic Tests: Please specify relevant investigations and tests (e.g. chest x-ray, echocardiogram, chest Computed Tomography, etc.) with name, date of tests and findings/values (please attach available reports):

_____

_____

_____

_____

_____

REPORTER Name: _____
State/Province: _____
Country/Postal Code: _____
Phone: (include country code): _____
Signature: _____
Title: _____ Date: _____

(TFuQ on Cytokine Release Syndrome version 2.1)